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NON-UNION IN LONG BONE FRACTURES: RISK FACTORS, PATHOPHYSIOLOGICAL MECHANISMS, AND EMERGING TREATMENT STRATEGIES

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ABSTRACT
Long bone non-union is a major complication of fracture healing that leads to prolonged disability, repeated surgical interventions, and considerable socioeconomic burden. Its development is influenced by complex interactions among biological, mechanical, vascular, inflammatory, and patient-related factors that disrupt the normal fracture healing process. This review examines the current evidence on the biology of fracture healing, the pathophysiological mechanisms underlying non-union, and the major patient-, fracture-, surgical-, and infection-related risk factors associated with impaired bone regeneration. The clinical role of contemporary imaging modalities, including conventional radiography, computed tomography, magnetic resonance imaging, nuclear medicine techniques, and emerging artificial intelligence-assisted imaging, is discussed with emphasis on their applications in diagnosis, treatment planning, and monitoring of fracture healing. Current management strategies involving mechanical stabilization, biological augmentation, and physical stimulation therapies are reviewed together with emerging regenerative approaches, including stem cell therapy, tissue engineering, biomaterial-based scaffolds, gene and RNA therapeutics, exosome-based interventions, nanomedicine, and three-dimensional bioprinting. Current challenges related to clinical translation, standardization of treatment protocols, precision medicine, biomarker-guided decision making, and artificial intelligence are also highlighted. Collectively, these advances provide valuable opportunities to improve diagnostic accuracy, optimize individualized treatment strategies, and enhance long-term functional outcomes in patients with long bone non-union..

KEYWORDS: Long bone non-union; Fracture healing; Diagnostic imaging; Bone regeneration; Regenerative medicine

INTRODUCTION
Fractures of long bones, including those of the femur, tibia, humerus, radius, and ulna, account for the highest numbers of musculoskeletal injuries globally. Despite the biological and mechanical processes involved in the healing of fractures, some cases progress to delayed or non-union of fracture, characterized by persistent pain, disability, and loss of functionality (Mills et al., 2017). Non-union is a situation where a fracture fails to heal within the expected period without requiring any further measures. Non-union remains an unaddressed problem in orthopedic trauma surgery (Bowers & Anderson, 2024). It subjects patients to multiple surgeries and rehabilitation programs, resulting in a reduced quality of life (Nicholson et al., 2021). The healing of a fracture is dependent on various biological, mechanical, vascular, and immunological processes; any interruption of these processes prevents bone regeneration (Bahney et al., 2019; Einhorn & Gerstenfeld, 2015). About 5-10% of all fractures develop into delayed or non-unions. The percentage of non-union fractures is even higher in cases of open fractures, high energy fractures, or tibia and femur fractures (Mills et al., 2017; Zura et al., 2017). Increasing incidence of road traffic accidents, sport injuries, osteoporosis, and elderly population further increase the burden of long bone fractures. Fracture-related infection and certain diseases such as diabetes mellitus and chronic kidney disease affect the healing process by interfering with bone metabolism, vascularisation, and immunity (Metsemakers et al., 2024; Hofbauer et al., 2022; Faraj & Napoli, 2025).
Long bone non-union is another issue which causes significant financial and social burden due to multiple surgical interventions, prolonged hospital stay, sophisticated imaging, biological enhancement, and long-term rehabilitation period

(Vanderkarr et al., 2023). Chronic pain, limited range of movements, muscle wastage, malalignment of limbs, and inability to walk affect patients' ability to perform independently and negatively influence their quality of life (Bowers & Anderson, 2024). Non-union diagnosis may be difficult to make relying on clinical criteria alone. Therefore, imaging is necessary to confirm non-union presence, assess the fracture stability, implants integrity, and other related issues, such as infections and bone defects (Cunningham et al., 2017; Schwarzenberg et al., 2020). Although radiography still remains the main imaging technique, there has been considerable progress in CT, MRI, nuclear medicine methods, and artificial intelligence imaging (Hosny et al., 2018; Yasaka & Abe, 2018). Effective management needs restoration of the biological and mechanical environment through stable fixation, infection prevention, and biological enhancement, despite the absence of any standard treatment approaches (Schlickewei et al., 2019; Nicholson et al., 2021).

New developments in osteoimmunology, regenerative medicine, biomaterial sciences, musculoskeletal imaging, and new technologies have significantly increased knowledge about the treatment of long bone non-unions. The aim of this review is to provide an overview of the current evidence on the biology and pathophysiological mechanisms of long bone non-union, identify the major patient, fracture, surgical, and infection-related risk factors, evaluate contemporary diagnostic imaging modalities and management strategies, and highlight emerging regenerative therapies and future directions for improving clinical outcomes.

2. Biology of Normal Fracture Healing

Fracture healing is a complex regenerative process involving coordinated biological, cellular, and mechanical events that restore the structural integrity and functional properties of bone following injury. In contrast to other tissues, bone possesses the unique ability to regenerate without scar formation under appropriate biological and mechanical conditions. The healing process involves coordinated inflammatory responses, progenitor cell recruitment, angiogenesis, and mechanobiological signaling. Impairment of these processes may lead to delayed healing or non-union. Fracture healing progresses through three sequential biological stages that are supported by coordinated cellular and molecular regulatory mechanisms. The biological stages of fracture healing and their key regulatory components are summarized in Table 1.

Table 1. Biological stages and key regulators of normal fracture healing

Biological Components	Major Biological Events	Principal Cells/Mediators	Clinical Significance	Study
Inflammatory phase	Hematoma formation, Inflammatory response, Cytokine release	Platelets, Neutrophils, Macrophages, MSCs	Initiates tissue repair, Recruits progenitor cells	Molitoris et al. (2024)
Reparative phase	Soft callus formation, Angiogenesis, Woven bone formation	MSCs, Chondrocytes, Osteoblasts, VEGF	Restores fracture stability, Promotes new bone formation	Bahney et al. (2019); Wu et al. (2024)
Remodeling phase	Replacement of woven bone with lamellar bone	Osteoblasts, Osteoclasts	Restores bone architecture, Improves mechanical strength	Thompson et al. (2015); Boyle et al. (2003)
Cellular regulation	Osteogenic differentiation and matrix synthesis	Mesenchymal stem cells	Supports skeletal regeneration, Enhances callus formation	Brown et al. (2024); Oryan et al. (2020)
Molecular regulation	Angiogenesis, immune regulation, mechanotransduction	VEGF, RANK/RANKL /OPG, Immune cells	Coordinates bone remodeling, Regulates fracture healing	Schipani et al. (2009); Ikebuchi et al. (2018); Uzer et al. (2016)

As summarized in Table 1, normal fracture healing consists of three sequential biological stages: inflammatory, reparative, and remodeling, supported by coordinated cellular and molecular regulatory mechanisms. The stages of fracture healing and their underlying regulatory processes are discussed in the following sections.

2.1 Stages of Fracture Healing

Fracture healing progresses through three interconnected stages: inflammation, repair, and remodeling (Buza III & Einhorn, 2016; Pountos & Giannoudis, 2018). Although these stages overlap temporally, each performs distinct biological functions that collectively restore skeletal integrity. The inflammatory stage begins immediately after injury with hematoma formation and activation of inflammatory cells. Platelets, neutrophils, and macrophages release cytokines and growth factors that remove damaged tissue, recruit mesenchymal stem cells, and stimulate angiogenesis, thereby establishing the biological environment required for subsequent fracture repair (Molitoris et al., 2024). During the reparative stage, mesenchymal stem cells differentiate into chondrocytes and osteoblasts, leading to the formation of a soft callus followed by its mineralization into woven bone. Angiogenesis restores vascular supply and supports extracellular matrix deposition, while mechanical stability facilitates successful callus maturation (Bahney et al., 2019;

Wu et al., 2024). The remodeling stage involves the replacement of immature woven bone with mature lamellar bone through coordinated osteoblastic bone formation and osteoclastic bone resorption. This process restores the normal cortical architecture and medullary canal while adapting bone to physiological loading conditions (Thompson et al., 2015).

2.2 Cellular and Molecular Regulation

Healing of fractures requires a coordinated interaction between several different cell types, signaling molecules, and biomechanical stimuli. Mesenchymal stem cells have emerged as the major progenitor cells responsible for fracture healing. In response to injuries, mesenchymal stem cells migrate to the injured areas where they proliferate and differentiate into osteoblasts and chondrocytes thus leading to callus formation and regeneration of bone. Their regenerative potential has made them an attractive option for the treatment of impaired fracture healing (Brown et al., 2024; Oryan et al., 2020). Osteoblasts form and mineralize bone matrix whereas osteoclasts degrade damaged and immature bone during remodeling. The coordinated function of these cells is controlled by the RANK/RANKL/OPG signaling system (Ikebuchi et al., 2018; Boyle et al., 2003). The immune cells such as macrophages and lymphocytes control inflammation, stem cell recruitment, and tissue regeneration. At the same time, the angiogenesis process, controlled mainly via VEGF signaling, ensures restoration of blood supply necessary for oxygen transport and callus formation. In parallel, the process of mechanotransduction provides the osteocytes and other bone cells the ability to transduce mechanical signals into biological ones controlling osteogenesis. Proper mechanical stimulation leads to a good outcome, while lack of stability affects signaling processes and causes the risk of non-unions (Schipani et al., 2009; Uzer et al., 2016; Claes, 2022).

3. Pathogenesis of Long Bone Non-Union

Non-union of long bones occurs when there is a breakdown in the synchronized biological and mechanical activities needed for proper bone repair. Non-union does not occur due to a single abnormality but rather through a complex interplay between poor bone formation, mechanical instability, ongoing inflammation, infection, and disrupted signaling. The disruptions in these factors prevent callus formation, mineralization, angiogenesis, and bone remodeling, thus leading to an inability to consolidate the fracture. Knowledge of these processes gives the biological basis of the approaches that can be used to diagnose and treat the problem. Of the various factors above, one that has a great importance in fracture healing is molecular signaling. Figure 1 shows the important signaling pathways in fracture healing.

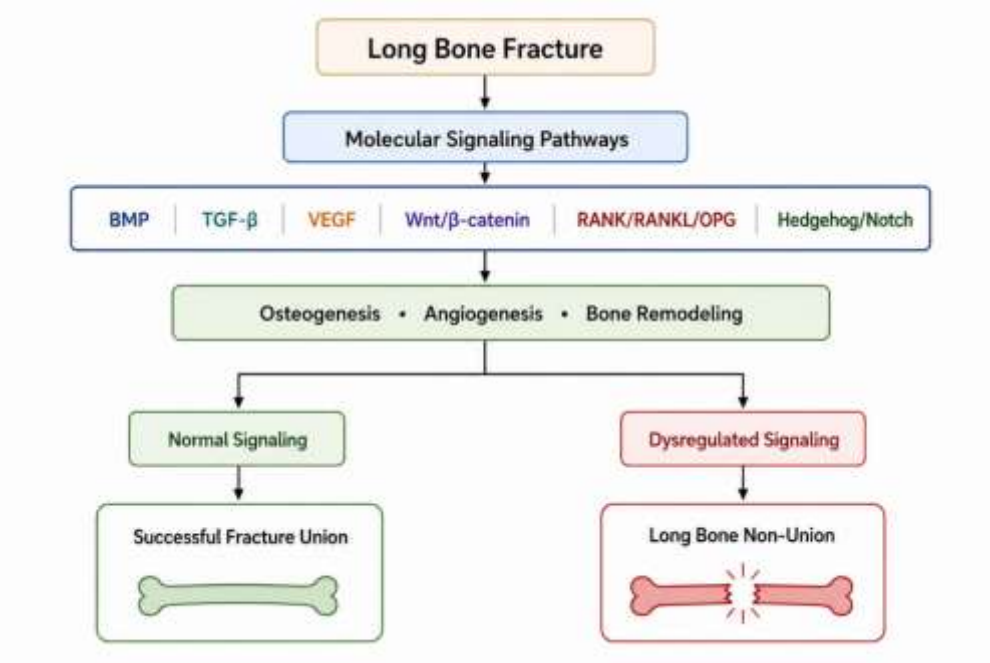

Figure 1. Key molecular signalling pathways regulating fracture healing and long bone non-union

As demonstrated in Figure 1, activation of BMP, TGF-β, VEGF, Wnt/β-catenin, RANK/RANKL/OPG, and Hedgehog/Notch signaling pathways ensures osteogenesis, angiogenesis, and bone remodeling, thus contributing to successful fracture union. On the other hand, deregulation of these signaling pathways causes disruption of the above-mentioned processes and leads to the formation of non-unions. Major pathogenic factors underlying long bone non-unions are described below.

3.1 Biological Failure

Biological failure is considered one of the primary processes causing long bone non-union. Reduced osteogenesis hampers the ability of osteoprogenitor cells to generate mineralized bone tissue and, therefore, results in insufficient callus formation. Furthermore, impairment of mesenchymal stem cells prevents them from proliferation and migration as well as differentiation into osteoblasts and chondrocytes, which in turn prevents skeletal regeneration (Schlickewei et al., 2019; Bowers & Anderson, 2024). Inflammation causes disruption of the healing process by maintaining high levels of pro-

inflammatory cytokines, which prevent differentiation and generation of extracellular matrix. Besides, deficient angiogenesis fails to provide enough nutrients to the fracture site and forms an unfavorable environment for bone regeneration, causing delayed union or even non-union (Chang et al., 2020; Cunningham et al., 2017).

3.2 Mechanical Failure

An ideal mechanical environment with adequate stability but sufficient physiological loads is crucial for the healing process. Excessive instability, interfragmentary strain, and fixation failures result in impaired cellular organization and mineralization of the callus, thus disrupting healing and slowing down the ossification process. Implant-related problems, such as fixation failure, loosening of hardware, and loss of fracture reduction also undermine the biomechanical stability and lead to a high risk of non-union. Hence, proper fixation and careful pre-surgical planning remain vital factors for successful fracture management (Claes, 2022; Maceroli et al., 2017).

3.3 Infection-Associated Non-Union

Infection related to the fractures is one of the main reasons for non-union since bacteria stimulate inflammation and impede bone regeneration. The microorganisms attach themselves to the implants and form biofilms protecting them from the host immune response and treatment. Besides, chronic osteomyelitis leads to further damage to the bone and soft tissues, prolonging the inflammatory processes and impairing vascularization. Dysregulated immune responses may contribute to tissue destruction and impede the repair process. Thus, eradication of the infection is essential for fracture healing (Zimmerli & Sendi, 2017; Vanvelk et al., 2023; Metsemakers et al., 2024).

3.4 Molecular Signaling Pathways

Fracture repair involves the interaction between several signaling pathways that coordinate proliferation, differentiation, angiogenesis, and bone remodeling processes. BMP pathway promotes osteogenic differentiation and extracellular matrix deposition, while TGF-β signaling pathway controls osteoprogenitors recruitment and matrix synthesis. Osteogenic signaling via Wnt/β-catenin signaling promotes osteoblast maturation and maintenance of skeletal homeostasis, whereas VEGF signaling pathway is responsible for neovascularization and is essential for callus formation. Further control of bone remodeling processes involves the regulation of RANK/RANKL/OPG pathway that provides balance between osteoblasts and osteoclasts activities. Some other developmental pathways such as Hedgehog signaling and Notch signaling pathways affect osteogenic differentiation and regeneration of bone tissue. Moreover, some novel molecular markers will provide an opportunity for early diagnosis of delayed healing of bone fractures (Hu et al., 2024; Sen et al., 2026; Yasaka & Abe, 2018).

4. Risk Factors for Long Bone Non-Union

Non-union of long bones is a complex disorder that results from various factors like patients' features, the degree of fracture, surgical treatment, and infections. Such features can interfere with biological and mechanical factors involved in fracture healing, making non-union of long bone more probable. Detection of such risk factors that can be modified and not modified at the beginning is very important for planning treatment and prevention measures. Major risk factors of long bone non-union are listed in Table 2.

Table 2. Major risk factors associated with long bone non-union

Category	Representative Risk Factors	Primary Effect on Healing	Key References
Patient-related	Age, diabetes, osteoporosis, smoking, obesity, malnutrition	Reduced osteogenesis, impaired vascularity, altered metabolism	Zura et al. (2016); Hofbauer et al. (2022); Pearson et al. (2016)
Fracture-related	Open fracture, high-energy trauma, bone loss, severe soft-tissue injury	Increased tissue damage and delayed callus formation	Halvachizadeh et al. (2023); Mills et al. (2017)
Surgical/mechanical	Poor fixation, implant failure, inadequate reduction, instability	Excessive interfragmentary motion and impaired union	Maceroli et al. (2017); Claes (2022)
Infection-related	Biofilm formation, chronic osteomyelitis	Persistent inflammation and compromised bone regeneration	Metsemakers et al. (2018); Zimmerli & Sendi (2017)

As given in Table 2, long bone non-union occurs due to the complex interplay of multiple factors related to the patient, fracture, surgery, and infection rather than the presence of a single one. The proportion of each of these risk factors varies between patients and has an impact on the biological and mechanical environments needed for proper healing. The next section covers the major types of risk factors and their importance for the occurrence of long bone non-union.

4.1 Patient-Associated Risk Factors

There are many patient-associated risk factors that negatively affect bone repair by influencing bone metabolism, vascularity, and immune response. With aging, the osteogenic capacity decreases and leads to delayed tissue regeneration, whereas diabetes causes the inhibition of angiogenesis and collagen production, and hence impaired callus formation (Zura et al., 2016; Hofbauer et al., 2022). Osteoporosis reduces bone quality and stability of the fixator, and smoking inhibits vascularization and osteoblasts' work (Pearson et al., 2016; Chang et al., 2020). Additionally, obesity, nutritional

deficiencies, vitamin D insufficiency, chronic kidney disease, and immunological conditions affect the process of bone fracture healing (Faraj & Napoli, 2025; Greene et al., 2025).

4.2 Fracture-Related Factors

The features of fracture significantly affect healing. Open fractures, high energy trauma, and segmental bone loss are characterized by considerable damage of tissues, impaired vascularity, and a higher risk of infection, thus contributing to delayed bone regeneration (Halvachizadeh et al., 2023). The same applies to severe damage of soft tissues and bones of anatomically fragile areas such as tibia due to limited vascularity and difficulty in biomechanics (Mills et al., 2017; Nicholson et al., 2021).

4.3 Factors related to Surgery and Mechanics

Proper surgery is important for effective bone healing. The improper strategy of fixation, wrong choice of implants, bad reduction of fracture, and unstable fixation may lead to excessive movement between fragments, impaired maturation of callus and non-union (Maceroli et al., 2017; Claes, 2022). Thus, preoperative planning and proper fixation still play an important role in the process of biological repair.

4.4 Infection and Microbiological factors

Infection complicates bone healing through prolonged inflammation, biofilm formation, and chronic osteomyelitis. The biofilm protects microorganisms from immunologic response and antibiotic treatment and increases the chances of non-union due to difficult infection treatment (Metsemakers et al., 2018; Zimmerli & Sendi, 2017). Hence, diagnosis and prevention of infection are important steps in non-union treatment.

4.5 Predictive Models and Risk Stratification

Prediction models of risk take into consideration the risk factors associated with patients, fractures, and treatments in order to determine the patients who have an elevated risk of developing non-union complications. This can enhance clinical results because the models help in the customization of care and early detection (Vanderkarr et al., 2023; Bowers & Anderson, 2024).

5. Radiological Evaluation and Diagnostic Imaging of Long Bone Non-Union

Radiological evaluation is critical in the diagnosis of non-union of long bones, assessment of fracture healing process, identification of possible complications, and development of treatment strategy. Radiology provides objective data in addition to the clinical findings regarding fracture stability, callus formation, implant condition, bone vascularity, and infection. Innovations in cross-sectional imaging, functional imaging, and artificial intelligence increased the accuracy and personalization of diagnostics and management. Major diagnostic imaging techniques in the assessment of non-union of long bones are discussed below.

5.1 Clinical Application of Diagnostic Imaging

Diagnostic imaging is an integral part of the treatment of long bone non-union at each step from establishing the diagnosis and planning surgery to the evaluation of the healing process after surgery. Proper use of imaging allows assessing the state of fracture alignment, maturation of callus, stability of implants, cortical continuity, biological activity, and early complication such as infection or implant failure (Cunningham et al., 2017; Schwarzenberg et al., 2020).

5.2 Imaging Modalities for Long Bone Non-Union Evaluation

There are various imaging methods that can be utilized to assess non-union of the long bones, all of which offer complimentary information related to structure, function, and biology. The choice of the right imaging method depends on the clinical presentation of the problem, potential complications, and the particular objectives for the diagnosis. Figure 2 illustrates some of the common imaging methods for non-union of the long bones and their diagnostic uses.

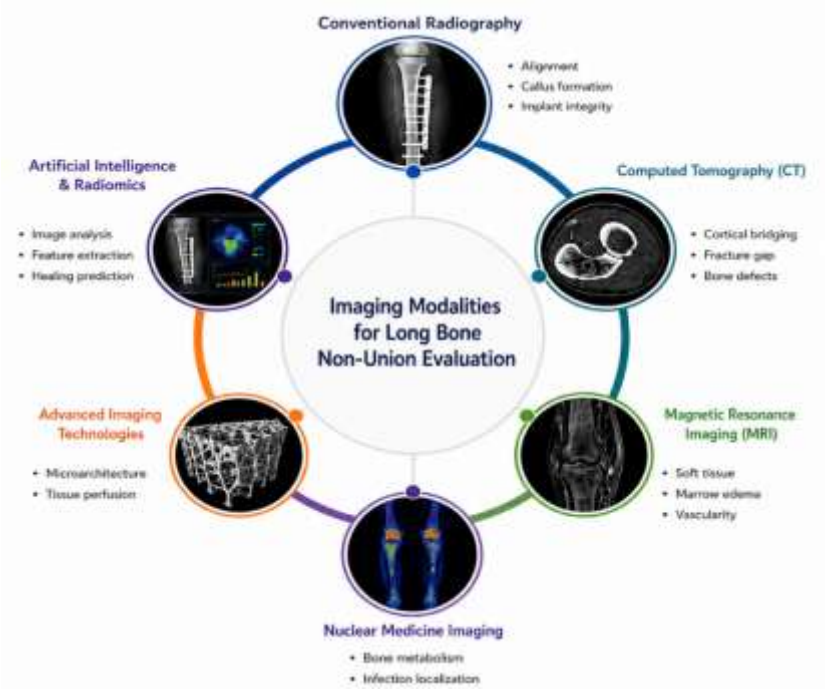

Figure 2. Imaging Modalities for Long Bone Non-Union Evaluation

As given in Figure 2, conventional radiography is used as the first-line imaging technique, while CT, MRI, nuclear medicine imaging, new imaging techniques, and image analysis using artificial intelligence provide additional structural, functional, and quantitative information for the comprehensive evaluation of bone healing and long bone non-unions. Below, the respective imaging techniques and their applications are described.

5.2.1 Conventional Radiography

Radiography is still used as the first-line imaging technique due to its widespread availability, cost-effectiveness, and capability to show fracture alignment and callus formation. Radiographic signs of bone healing are bridging cortex, obliteration of the fracture line, and increasing mineralization, while non-healing is indicated by persistent gap between the fragments, no callus formation, loosening, or failure of the implanted hardware. Although possessing such advantages, conventional radiography is limited in its sensitivity in early stages of bone healing and in evaluating complex fractures (Schwarzenberg et al., 2020; Cunningham et al., 2017).

5.2.2 Computed Tomography (CT)

CT is excellent for visualizing cortical bone and especially helpful when the radiographic assessment is equivocal. CT is capable of evaluating the status of cortical bridging, morphology of the fracture gap, position of the implant, and osseous defects; hence, it is very helpful in the pre-operative planning of complicated non-unions. Current advances in ultra-low dose CT have enhanced its image quality while limiting radiation exposure (Konda et al., 2018).

5.2.3 Magnetic Resonance Imaging (MRI)

MRI has good soft tissue contrast properties and is able to assess bone marrow edema, surrounding musculature, tendons, and neurovascular structures. MRI is especially useful in the detection of occult infections, marrow viability, and vascularity in cases of suspected avascular non-union. This gives biologic information that cannot be provided by radiographs (Fritz et al., 2015).

5.2.4 Nuclear Medicine Imaging

Functional imaging can be used in order to determine bone metabolism and inflammation. Bone scintigraphy helps to assess bone turnover, while SPECT/CT uses information about bone metabolism and anatomy in order to enhance the localizing ability. PET/CT provides better diagnosis since it identifies infections and inflammation in complex fracture infections and complications associated with implants (Palestro, 2016; Palestro et al., 2021; Palestro, 2023).

5.2.5 Advanced Imaging Technologies

Innovative imaging technologies help to assess fracture healing not only from the standpoint of its structure but also on the basis of biological factors. While dual energy CT is helpful in improving tissue characterization and reduces artifacts around metallic implants, quantitative CT and HR-pQCT allow for assessing bone microstructure and mineral density. DCE-MRI allows for assessing tissue perfusion and vascularization (Schwarzenberg et al., 2020).

5.2.6 Artificial Intelligence and Radiomics

Artificial Intelligence and radiomics are changing musculoskeletal imaging through the automation of imaging analysis, feature extraction, and prediction of fracture healing outcome. Machine learning can help physicians identify imaging features linked with delayed union and non-union, while deep learning can aid in fracture detection and management plans. This technology could possibly be used for precision medicine via risk prediction and clinical decision support in the future, though it needs validation before any clinical application (McBee et al., 2018; Hosny et al., 2018; Yasaka & Abe, 2018; Topol, 2019).

6. Contemporary Management Strategies

The management of long bone non-union is aimed at reestablishing both the biological and mechanical environment required for proper bone repair. The choice of treatment method is influenced by the kind of non-union, the characteristics of the fracture, patient related risk factors, and presence of infection or bone loss. Current methods of managing non-union utilize stable fixation, biological enhancement and physical stimulation methods. The major management approaches used in long bone non-union are outlined in Table 3 below.

Table 3. Contemporary management strategies for long bone non-union

Management strategy	Primary objective	Clinical application	Key references
Mechanical optimization	Restore fracture stability	Exchange nailing, plating, external fixation	Nicholson et al. (2021); Buza & Leucht (2018)
Biological augmentation	Enhance osteogenesis	Bone grafts, BMPs, PRP, BMAC	Piuzzi et al. (2018); Hernigou et al. (2022)
Bone substitute materials	Restore bone defects	Synthetic and biological substitutes	Plantz et al. (2021); Pountos & Giannoudis (2016)
Physical stimulation	Promote bone regeneration	LIPUS, PEMF, ESWT	Khalifeh et al. (2018); Bhandari et al. (2016)

Successful management of non-union in long bones often involves the use of mechanical stability and biological enhancement as described in Table 3. The following paragraphs outline some of the common management techniques employed in clinical practice today.

6.1 Principles of Non-Union Management

Identification of the cause of non-union is essential in developing a suitable plan for managing the condition. It may include any of biological impairment, mechanical instability, infection, or even a combination of these. Treatment will therefore involve treating any infection that exists, stabilizing the fractures, enhancing biological environment and patient risk factors prior to definitive reconstruction (Nicholson et al., 2021; Bowers & Anderson, 2024).

6.2 Mechanical Optimization

Stabilization of the injury mechanically is important for the healing process of fractures since movement between fragments inhibits maturation of callus. Exchange intramedullary nailing can still work in the management of non-unions that lack infections especially in the diaphysis of long bones to increase stability and enhance healing from the inner side of the bones. Compression plating offers stable fixation and malalignment correction while external fixation and circular frame techniques work best in cases of infections, bone defects, and correction of deformities. Appropriate implant selection and restoration of the mechanical axis remain critical determinants of treatment success (Buza & Leucht, 2018; Nicholson et al., 2021).

6.3 Biological Augmentation

Biological augmentation increases the regenerative capability of the fracture region through stimulation of bone formation and improvement of biological conditions at the site. The use of autografting is considered to be the golden standard due to the osteogenic, osteoinductive, and osteoconductive effects of this procedure (Pountos & Giannoudis, 2016). When autograft availability is limited, allografts and synthetic bone substitute materials provide structural support for bone regeneration (Plantz et al., 2021). Bone morphogenetic proteins (BMPs), platelet-rich plasma (PRP), and bone marrow aspirate concentrate (BMAC) have demonstrated promising clinical outcomes by enhancing cellular proliferation, angiogenesis, and new bone formation, particularly in challenging non-unions (Piuzzi et al., 2018). Clinical data obtained recently confirm the efficacy of bone marrow aspirate concentrate as biological aid in treatment of complicated fractures of long bones (Hernigou et al., 2022).

6.4 Physical Stimulation Therapies

Stimulation physical therapy has been developed as a non-invasive technique to support bone healing processes. While LIPUS promotes cellular growth and matrix formation through mechanotransduction, PEMF therapy facilitates bone growth and mineralization. Another form of stimulation therapy that has shown efficacy is extracorporeal shockwave therapy (ESWT), which increases vascularization and bone regeneration. Though they can be considered a replacement for surgical treatments in established non-union cases, these methods can serve as useful adjuncts for specific cases (Khalifeh et al., 2018; Bhandari et al., 2016).

7. Emerging Therapeutic Strategies

The current developments in fields such as regenerative medicine, biomaterial science, molecular biology, and digital health technologies have broadened the scope of treatment modalities for long bone non-union. The modern treatment methods are quite different from the traditional treatments in that they are geared towards improving the biological milieu rather than achieving mechanical stability. They involve the promotion of osteogenesis, angiogenesis, immune modulation, and tissue regeneration. Figure 3 summarizes the major emerging therapeutic strategies currently being explored for enhancing bone regeneration and improving clinical outcomes in long bone non-union.

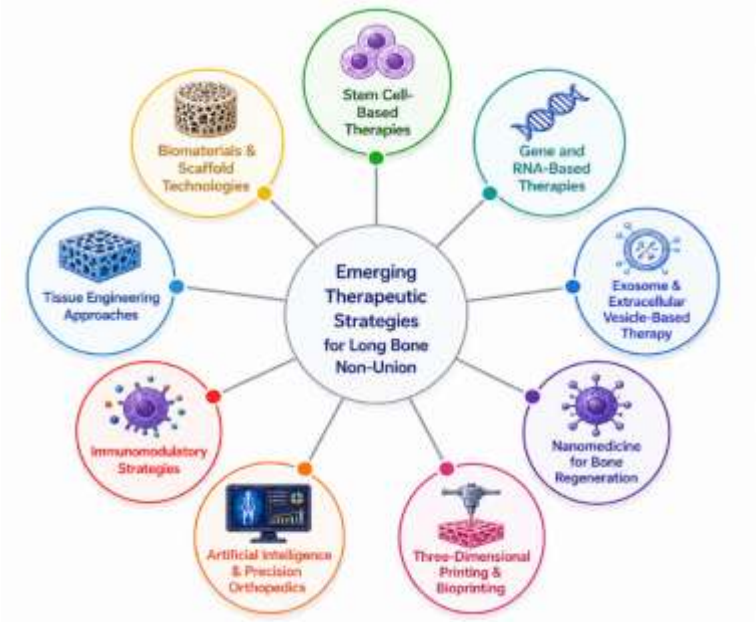

Figure 3. Emerging therapeutic strategies for long bone non-union

As shown in Figure 3, novel treatment modalities are quite diverse and include various methods of regeneration such as stem cell therapy, tissue engineering, biomaterials and scaffolds, gene and RNA therapy, exosome therapy, immunomodulation therapy, nanomedicine, 3D printing and bioprinting, as well as artificial intelligence-assisted orthopedics. All of these novel treatment modalities have one common goal, which is improving biological healing and speeding up fracture healing in order to achieve personalized treatment of non-unions of the long bones. Individual treatment modalities are presented in below subsections.

7.1 Stem Cell-Based Therapies

Stem cell-based therapies have been widely discussed as a result of their potential to regenerate bones via osteogenic differentiation and paracrine effect. Bone marrow-derived or adipose-derived mesenchymal stem cells improve callus formation, induce angiogenesis and influence the local inflammation. The latest clinical trials revealed promising results after transplants of expanded mesenchymal stromal cells along with osteoconductive biomaterials for the therapy of atrophic long bone non-union (Orozco Delclós et al., 2024).

7.2 Tissue Engineering Strategies

Bone tissue engineering involves stem cells, bioactive agents, and biomaterials, which provide an opportunity to create a microenvironment for bone regeneration. Tissue engineering constructs stimulate cellular proliferation, matrix synthesis and formation of vasculature while providing a temporary structure during the bone formation process. Experimental studies keep proving the possibility of the use of tissue engineering constructs for critical-size bone defect and complex non-unions repair (Mukhopadhyay et al.; O'Brien, 2011).

7.3 Biomaterials and Scaffold Technologies

Modern biomaterials have progressed from being just simple materials that act as structure replacements to more advanced bioactive scaffolds that are able to modulate cell behavior and regenerate tissues. These bioactive scaffolds are developed to mimic the natural bone extracellular matrix, and also they increase osteoconductivity, biodegradability, and controlled release of bioactive substances. Antimicrobial nanoparticle-containing and microRNA-carrying multifunctional scaffolds have demonstrated remarkable regenerative abilities and antibacterial activity for treating difficult bone lesions (Sadowska et al., 2024).

7.4 Gene and RNA-Based Therapies

The gene therapy is a prospective approach that could help to improve bone healing by controlling osteogenic signaling pathways. The introduction of genes that code osteogenic growth factors or other RNAs might result in stimulation of bone formation, angiogenesis, and tissue regeneration. RNA-based therapies, such as microRNA delivery, are also promising tools for regulation of cellular differentiation and bone remodeling during impaired bone healing process (Bougioukli et al., 2018).

7.5 Exosomes and Extracellular Vesicle-Based Therapy

Exosomes and extracellular vesicles have been found to be useful regenerative therapies that help deliver proteins, growth factors, mRNA, and microRNA to their target tissues. Biological vesicles improve osteoblasts' differentiation, angiogenesis, and extracellular matrix synthesis while decreasing inflammatory reactions. Their use in conjunction with

biomaterial scaffolds has further increased their efficacy in experimental models of bone regeneration therapy (Li et al., 2018; Yan et al., 2020).

7.6 Immunomodulatory Strategies

Advances in osteoimmunology have indicated that modulating immune reaction is one more way to improve the healing of fractures. Modulation of macrophage polarization, inflammatory cytokine secretion, and interactions of immune cells may facilitate shifting from inflammation stage to regeneration stage without causing chronic inflammation that leads to non-union formation. These strategies are increasingly recognized as complementary approaches to conventional orthopedic interventions (Molitoris et al., 2024).

7.7 Nanomedicine for Bone Regeneration

The advent of nanotechnology has made possible the invention of highly advanced delivery systems which can be used to promote osteogenesis, angiogenesis, and release of drugs. The use of nanoparticle-based biomaterials helps in cell adhesion, proliferation, and differentiation, while providing a means to deliver growth factors and drugs. Recent developments have shown great promise in using nanomedicine to enhance bone regeneration and repair of complicated bone injuries (Farjaminejad et al., 2024; Liang et al., 2024).

7.8 Three-Dimensional Printing and Bioprinting

Three-dimensional printing and bioprinting have revolutionized personalized orthopedic reconstruction through patient-specific implant and scaffold design. This technology facilitates customization of scaffold design and mechanical properties, while enabling loading of cells and bioactive molecules, and thus providing ways to customize bone regeneration techniques for complicated non-unions (Murphy & Atala, 2014).

7.9 Artificial Intelligence and Precision Orthopedics

The use of artificial intelligence has become more common in the field of orthopedics for the purposes of fracture classification, prediction of healing outcomes, surgical planning, and individualization of the treatment plan. Machine learning methods can process clinical, imaging, and biological information to predict the patients' risks for non-union and develop an optimal strategy for therapy (Topol, 2019).

8. Challenges and Future Perspective

Non-union of long bones continues to be a major clinical problem even though there has been a lot of development in the sphere of biological mechanisms of the disease and treatment options. There are still many difficulties in the translational process due to the complicated mechanism of bone healing, patient heterogeneity, and individual response to treatment. Even though there were promising results in experiments with regenerative treatments, their broad implementation is limited by various factors including different designs of the studies, patient selection, regulation of the treatment, manufacturing process, costs, and safety of the procedure. Moreover, lack of consensus on diagnosis criteria and uniformity of treatment approaches adds to the complexity of medical decision-making in different institutions and among surgeons. Moreover, there is no evidence for reliable biomarkers on molecular, biochemical, and imaging levels, which hinders the ability to predict poor fracture healing at an earlier stage.

Future treatment approaches of long bone non-union will rely heavily on the concept of precision medicine where the treatment methods can be tailored depending on the biology of the fracture, genetics of the patient, metabolism, mechanical demands, and individual clinical features of the patient. Clinical decision-making based on biomarkers could lead to early detection and better monitoring of treatment progress and personalized treatments. Artificial intelligence is also anticipated to have a major role in the evaluation of fractures, predicting the risks, planning treatment approaches, and monitoring of patients post-operatively by the incorporation of clinical, imaging, and biological information into intelligent decision support systems. Continuous improvement of regenerative therapy techniques along with multicenter clinical trials with standardized outcomes and follow-up periods will be necessary to generate clinical evidence. Collaboration between orthopedic surgeons, radiologists, biomaterial scientists, experts in regenerative medicine, and data scientists will help in transforming new technologies into personalized strategies for prevention and management of long bone non-unions.

9. CONCLUSION

Non-union of long bones is still one of the most difficult complications in orthopedic trauma because it involves many biological, mechanical, infectious, and patient-specific factors that interfere with the proper healing of the fractured bone. Progress in fracture biology research has revealed the importance of cellular interactions, molecular pathways, angiogenesis, and mechanotransduction for the regeneration of the bone tissue. At the same time, progress in imaging of fractures has significantly improved the ability to diagnose non-union, its characteristics, and develop treatment plans. Current methods of treatment focus on the combination of stable fixation and biological enhancement along with other treatment options. In addition, new methods such as stem cell therapy, tissue engineering, bio-scaffolds, gene and RNA therapy, exosome-based therapy, nanotherapy, and three-dimensional bioprinting have great potential to overcome the problems of traditional treatment. However, despite all these positive achievements, there are still some issues that need to be resolved with regards to the standardization of criteria, validation of new therapeutic approaches, and transition from experimental results to their practical implementation in clinics. All the future research in this field should be conducted

through the close cooperation of various disciplines, personalized therapy based on the use of biomarkers, introduction of artificial intelligence in clinical decision-making, and appropriately organized multi-center clinical trials.

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