



Review

Distraction Osteogenesis: A Comprehensive Review

Babapelumi Adejuyigbe ^{1,*} , Mohini Gharpure ², Charlotte F. Wahle ¹ and Jennifer R. Kallini ³¹ David Geffen School of Medicine, University of California, Los Angeles (UCLA), Los Angeles, CA 90095, USA² Medical College of Georgia, Augusta University, Augusta, GA 30912, USA³ Department of Orthopedic Surgery, University of California, Los Angeles (UCLA), Los Angeles, CA 90404, USA; jrkallini@mednet.ucla.edu

* Correspondence: badejuyigbe@mednet.ucla.edu

Abstract: Distraction osteogenesis (DO) is a process which uses the bone's natural healing tendencies to repair and lengthen pathologic, missing, or malformed bone. The mechanism of DO mimics the pathway that the body uses in any other fracture repair however the location of the fracture is carefully controlled by a surgical osteotomy. Postoperatively, the bone is allowed to begin its natural healing process, with the lengthener applying constant tension and thus re-initiating the process of healing along the length of the distraction gap. Current clinical indications for DO include limb length discrepancy, congenital bone length deformity, large bone defects, and extremity reconstruction due to hypoplasia or limb salvage procedures. The risks of DO include soft tissue complications, relapse or improper correction, cost or resource-related challenges, and psychosocial stigmas surrounding long treatment durations and the necessity of wearing the distraction lengthening hardware. Future directions for DO include supplements to the bone regeneration process (such as growth factors and/or mechanical stimulation) or improvements to the distractor device itself (changes in material and/or the structure of the device itself). This review aims to offer a comprehensive summary of the indications, underlying biological mechanisms, and practical considerations when implementing the use of distraction osteogenesis in clinical practice.



Citation: Adejuyigbe, B.; Gharpure, M.; Wahle, C.F.; Kallini, J.R. Distraction Osteogenesis: A Comprehensive Review. *Appl. Biosci.* **2024**, *3*, 503–516. <https://doi.org/10.3390/applbiosci3040032>

Academic Editors: Alessandro Pitruzzella, Alberto Fucarino and Fabio Bucchieri

Received: 4 October 2024

Revised: 19 November 2024

Accepted: 20 November 2024

Published: 21 November 2024



Copyright: © 2024 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

Keywords: distraction osteogenesis; bone regeneration

1. Introduction

Distraction osteogenesis (DO), colloquially known as “callotasis”, is an orthopedic surgical method which harnesses the body's natural bone healing process to lengthen hypoplastic or deficient bones [1]. This technique finds extensive clinical application in orthopedics across pediatric and adult populations, effectively addressing a spectrum of pathologic conditions including limb-length disparities, congenital bone deformities, significant bone defects secondary to trauma or infection, and malignant bone tumor resection [2–6].

In DO, macroscopic and microscopic processes occur simultaneously to drive bone regeneration across sequential phases—much in the same way that physiologic bone healing/regeneration occurs [1]. Physiologic bone healing is delineated by a framework of secondary fracture healing which includes (1) hematoma formation and inflammatory response, (2) soft callus formation, (3) hard callus synthesis, and (4) bone remodeling [7]. DO is similarly delineated by (1) osteotomy, (2) distraction lengthener application, (3) latency, (4) distraction, and (5) consolidation [2,8]. These phases rely on coordinated interactions between mechanical forces at the macroscopic level and molecular signaling pathways at the microscopic level [1,8,9].

Though similar, DO differs from physiologic bone healing in two distinct ways. Firstly, DO has the advantage of being activated by a controlled microtrauma, wherein a deliberate osteotomy triggers the bone's innate regenerative response. This controlled stimulation enables precise control over the rate and direction of bone growth, facilitating the correction

of skeletal deformities or defects [2,7,10,11]. Secondly, the mechanism of ossification in DO primarily follows a membranous pathway, wherein bone forms directly from mesenchymal cells without the intermediate step of cartilage formation, known as endochondral ossification. This distinction in the ossification process contributes to the unique characteristics and outcomes observed in DO compared to natural bone healing processes [7].

DO has allowed orthopedic surgeons to address complex skeletal conditions that were previously challenging to treat [2]. In the realm of pediatric orthopedics, DO is instrumental in treating limb length discrepancies, digital hypoplasia, angular deformities, and skeletal dysplasias [2,7]. In adults, it is used for cosmetic or post-traumatic limb lengthening and to restore function and esthetics following infection [2,7]. DO also plays a crucial role in reconstructive surgery in cases of nonunion, malunion, or segmental bone loss. Moreover, it is increasingly being employed in the management of oncologic conditions, allowing for limb salvage and restoration of function after tumor resection. The versatility of DO even extends beyond orthopedics, with emerging applications in craniofacial surgery and maxillofacial reconstruction [7].

While much of the existing literature focuses on the technical methodology/applications of DO in isolation, or through case studies, the aim of this paper is to provide an informative, comprehensive review of this orthopedic technique. This review seeks to bridge the gap between technical descriptions and broader clinical applications, offering a holistic understanding of DO. The paper begins by providing context regarding cellular and molecular components of DO, outlining the appropriate signaling pathways in each of its phases. An overview of the current clinical applications and outcomes within the field of orthopedics, ranging from limb length discrepancies to complex reconstructive procedures is also included. The risks and limitations associated with DO are also discussed below. Finally, this paper provides insights into the rapidly evolving future directions of research pertaining to this surgical technique, including a discussion of advancements in bone regeneration supplements and improvements in distractor devices.

By synthesizing the biological processes, current clinical applications, risks and limitations, and future prospects of DO, this review aims to serve as a comprehensive resource for clinicians and researchers, contextualizing the current state of DO within the broader landscape of orthopedic interventions and regenerative medicine.

2. Phases of Distraction Osteogenesis Through Molecular and Cellular Signaling Pathways

Distraction osteogenesis (DO) employs the underlying physiology of fracture repair to drive controlled bone healing. As a result, there are many overlapping principles between physiologic bone healing and DO. Both processes occur in sequential phases; however, it is important to note that many of these phases are not distinct and may be occurring simultaneously at different locations on the bone [7]. The phases of physiologic bone healing can be described through the framework of secondary fracture healing which includes (1) hematoma formation and inflammatory response, (2) soft callus formation, (3) hard callus synthesis, and (4) bone remodeling [7]. DO is also characterized by five sequential phases: (1) osteotomy, (2) distraction lengthener application, (3) latency, (4) distraction, and (5) consolidation. In each of these phases, there are delicate interplays between macroscopic and microscopic mechanisms which underpin bone modeling [7].

To outline how DO aims to leverage the naturally occurring steps of physiologic bone healing, it is essential to understand the underlying microscopic and macroscopic mechanisms of bone healing. When a bone fractures, it may heal through the processes of direct and/or indirect processes [7]. Direct healing is rarely naturally occurring, as it involves the two fractured ends being compressed together. As such, the principle which DO relies on is primarily indirect healing. The process of indirect healing begins with the bleeding that ensues after the insult to the bone (Figure 1). Within the early hematoma, local macrophages and inflammatory cells at the fracture site secrete cytokines IL-1, IL-6, and TNF- α , while mesenchymal cells and platelets produce growth factors FGF, PDGF, BMP, and TGF- β [2,7]. These signaling molecules further recruit inflammatory cells,

fibroblasts, and mesenchymal stem cells into the hematoma [2,7]. Osteoprogenitor cells (OPCs) mature into osteoblasts and osteocytes via BMP signaling and initiate hard callus formation in the subperiosteal region. Concurrently, undifferentiated mesenchymal stem cells form the cartilaginous soft callus in the hypoxic space between the fracture ends [2,7]. RANK-L expression increases in the soft callus, which stimulates osteoblast and osteoclast differentiation. As a result, the soft callus begins to calcify, forming the hard callus, and angiogenesis continues. The remodeling phase begins approximately 5 weeks after the fracture. Over the course of 3 to 6 months, the woven bone in the hard callus is converted to lamellar bone [2].

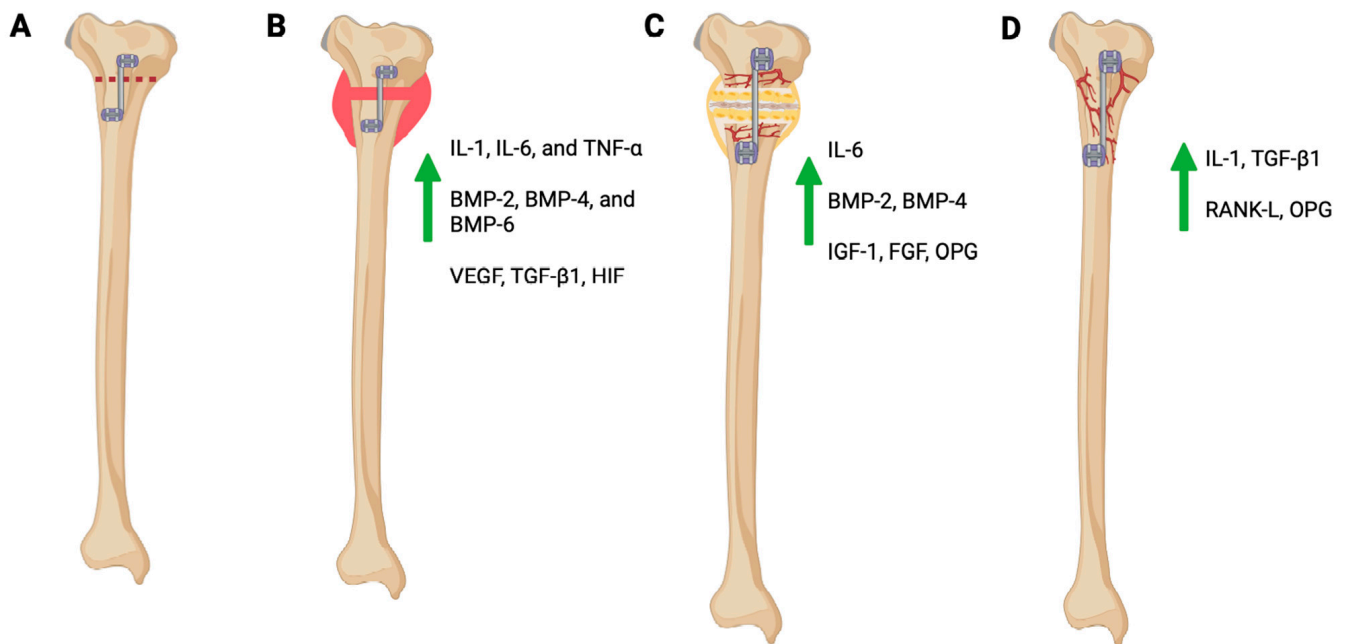


Figure 1. Signaling alterations during distraction osteosynthesis. Distraction osteosynthesis is divided into four steps. (A) An osteotomy is performed and a distractor is placed between the two fragments. (B) The latency phase begins with hematoma formation and the migration of cytokines and cell signals. (C) The distraction phase involves lengthening the bone each day, as chondrocytes and osteoblasts deposit matrix in the fibrous interzone. (D) The consolidation phase consists of remodeling the new bone into Haversian bone.

In DO, a fracture occurs via the initial surgical osteotomy. The distractor is placed, after which much of the bone's natural biology takes over. The "latency" step of DO maps on to step 1 of the primary process of indirect bone healing outlined above. A hematoma forms at the surgical osteotomy site, and an inflammatory response ensues, releasing many of the same inflammatory cytokines as a natural bone fracture. Next, just as with natural bone healing, soft callus begins to form in this step of DO [7]. After this point however the processes begin to diverge. This divergence is key, as it is important that the callus does not mature and thereby prevent subsequent elongation of the bone [12]. At this stage in DO, the distraction process ensues, providing a constant tension which functionally causes the bone to undergo microtrauma, thus repeating the cycle of inflammation followed by soft callus formation until the optimal length is achieved. Finally, after the conclusion of distraction, the bone is allowed to move on to consolidation which allows for mature bone to form, similar to the final stage of indirect bone healing [7]. This provides a broad overview of the mapping of the stages of DO onto innate bone healing; the intricacies of each of the steps of DO are discussed in more detail in Section 2 below.

2.1. Osteotomy

DO begins with a planned osteotomy to create two distinct, metabolically active bone segments. Classically, a transverse osteotomy is performed in the metaphysis of a long bone, with minimal periosteal stripping carried out to ensure that the bone remains viable [13,14]. The metaphysis in particular has the highest ratio of trabecular to cortical bone and therefore has the densest blood supply, thereby optimizing the chance of bridging bone formation/healing following distraction at the osteotomy site [14].

This phase in the DO process mimics the biology of a typical fracture undergoing indirect healing. Following trauma or osteotomy, there is rapid a migration of inflammatory cells secreting cytokines (IL-1, IL-6, and TNF- α) and growth factors (PDGF and TGF- β) [12]. These metabolically active sites are where subsequent bone healing will occur.

2.2. Distraction Lengthener Application

Prior to the osteotomy, the locations for distractor placement are determined based on desired length and vector direction. After the osteotomy, an external fixation system and pins are placed on either side of the osteotomy to maintain site stability.

a. Surgical Planning

- Pre-operative planning for DO must be meticulous and begins with a series of radiographs. Based on the radiographs, the precise location of the deformity can be determined and therefore the osteotomy planned for the apex of the deformity [15].
- One critical factor to evaluate pre-operatively is the axis. It is especially critical in DO use for certain clinical indications, such as angular deformity [10]. Pre-operative radiographs are used to draw out the normal axis of the bone and consider its location in relation to the joint or other nearby structures. Next, the degree of varus or valgus deformity can be appreciated in order to plan the optimal osteotomy and traction placement to correct the deformity [10].

Another critical factor in the clinical pre-operative planning of DO is the distraction index, or the rate at which the bone and soft tissue will optimally lengthen each day. The guidelines vary for this value by surgeon and by bone, but the typical range is from 1 to 2.5 mm/day [7,10,16–18]. While an initial rate can be determined during the planning phase, the distraction rate is also something that can be adjusted over time based on serial radiographs and clinical exam findings.

b. Selecting a Fixator

Originally, all DO fixators were relatively similar in structure. However, as research progresses, there are now several fixator models to select from, each with a set of advantages and disadvantages. The Ilizarov fixator was the first to be described by Professor Gavriil Abramovich Ilizarov in the early 1950s, and it was this innovation that set off the revolution of DO. The structure of the fixator was originally designed to treat tibial nonunion via two fixed, opposing compressive forces [10,11]. Soon thereafter, Ilizarov discovered the process of DO accidentally after observing callus formation when the two fixed rings were moved apart from each other (in distraction) instead of together (in compression) [10].

The design of the fixator is such that there are four circular rings (two in each bone on either side of the fracture/osteotomy site) which are fixed to the bone by screws and to each other by a series of connecting wires [10]. One advantage of the Ilizarov fixator is that it provides an optimal balance between rigidity and flexibility [14]. Having two rings fixed to each bone, each with two fixation points per ring, contributes significantly to the overall stability of the structure [10]. Other factors which can also contribute to the rigidity of the structure are the number of wires used for attachment and the radius of the wires [10]. The external nature of the fixed portions means that they can be placed precisely in the desired position depending on the indication and the bone. However, the system also has several drawbacks which are discussed in great detail in the “Risks and Limitations” section below.

With that said, the Ilizarov design remains the gold standard when it comes to DO and is still used very widely throughout the world [11].

One newer type of distraction lengthener that has been highly discussed in the recent literature is the utilization of a motorized or magnetic intramedullary nail that applies gradual internal traction forces for elongation [5,15,17,18]. This innovation is discussed in further detail below under the “Future Directions and Conclusions” section. The advantage of this newer development is lower rates of soft tissue infection and scarring with less external fixation [17–19]. The internal intramedullary method also often results in a shorter treatment time and decreased re-fracture risk [19]. The lack of external hardware can also make a non-trivial difference in patient satisfaction and quality of life given the long duration of treatment. However, this method also has drawbacks. One issue with the intramedullary technique is a higher degree of difficulty making minute adjustments without an external structure. In addition, this method is associated with longer operative time, increased intra-operative bleeding, and higher costs [17]. Additionally, though there is less risk of soft tissue breakdown or infection without an externally communicating structure, there is still a risk of intramedullary infection [17].

Aside from mechanical consideration in fixator selection, managing inflammation is an additional critical concept to consider. The inflammatory response associated with fixator placement can significantly impact the healing process and treatment outcomes. Maintaining an optimal balance between pro-inflammatory and anti-inflammatory cytokines (many of which will be discussed in Section 2.3) is essential for optimal bone healing [12–14]. To maintain such balance, the following several strategies are employed:

1. **Material selection:** Biocompatible materials such as titanium or stainless steel are preferred for fixator components to minimize foreign body reactions and excessive inflammation [20].
2. **Pin design and placement:** Optimizing pin design and careful placement can reduce soft tissue irritation and subsequent inflammatory responses. Hydroxyapatite-coated pins have shown promise in reducing pin site infections and inflammation [12,20].
3. **Tension adjustment:** Proper tension adjustment of the fixator wires helps distribute forces evenly, reducing localized stress and inflammation at pin sites.
4. **Pharmacological management:** In some cases, anti-inflammatory medications may be prescribed to modulate the inflammatory response, particularly during the early stages of treatment [12].
5. **Regular monitoring:** Frequent clinical and radiographic assessments allow for the early detection and management of excessive inflammation or infection [12].

By carefully considering these factors, clinicians can select and apply external fixators that effectively manage inflammation while promoting optimal bone regeneration during DO.

2.3. Latency

The beginning of this phase is marked by an inflammatory response, which ensues following the osteotomy. A hematoma immediately forms around the osteotomy site and contains immune cells releasing cytokines and signaling molecules. In addition to inflammatory cytokines (IL-1, IL-6, TNF- α) signaling mesenchymal stem cell (MSC) migration, hypoxia markers (TGF- β 1, HIF, VEGF, VEGFR, IL-10) promote new vessel formation and collagen I synthesis [12]. Approximately 24 h after the osteotomy, osteoid, or unmineralized bone tissue, deposits on the exposed bone ends [14]. Over the following days, MSCs transform into osteoprogenitor cells (OPCs) via BMP-2, BMP-4, and BMP-6 signaling, and the hematoma converts into a fibrous, soft callus that will serve as a scaffold for bone healing [12,13,21]. To avoid soft callus calcification and too much premature healing before the desired length is achieved, it is imperative that the latency phase does not exceed 5–10 days [7].

While the latency phase of DO is comparable to soft callus formation in fracture healing, there are differences in cytokine expression. In DO, the constant tension maintained by

the fixator promotes persistent IL-6 secretion, which slows OPCs' differentiation into osteoblasts [12]. This is beneficial because it allows continuous lengthening to occur without maturation of the callus or progression to consolidation. DO is also associated with a 2.5-fold increase in TGF- β 1 expression [7]. At physiologic levels, TGF- β 1 is typically involved in stimulating osteoblast proliferation. However, at the higher levels associated with this spike during DO, TGF- β 1 has been shown to suppress osteocalcin and prolong mineralization [12]. Finally, unlike natural bone healing, the transition to the next phase of DO relies on distractor activation.

In summary, the inflammatory response during the latency phase is characterized by a delicate balance between pro-inflammatory and anti-inflammatory cytokines. This balance is crucial for initiating the healing process while preventing excessive inflammation that could impair bone regeneration. Key aspects of cytokine expression and inflammation management during the latency phase include the following:

1. Pro-inflammatory cytokines: IL-1 β , TNF- α , and IL-6 are rapidly upregulated following osteotomy, initiating the inflammatory cascade and recruiting inflammatory cells to the site [8,12].
2. Anti-inflammatory cytokines: IL-10 and TGF- β are also expressed, helping to modulate the inflammatory response and prevent excessive tissue damage [8,12].
3. Growth factors: PDGF, VEGF, and BMPs are released, promoting angiogenesis and the recruitment of mesenchymal stem cells crucial for subsequent bone formation [8,12].
4. Cellular infiltration: Neutrophils, macrophages, and lymphocytes migrate to the osteotomy site, contributing to the removal of debris and the initiation of tissue repair [8,12].
5. Resolution of acute inflammation: Towards the end of the latency phase, the acute inflammatory response begins to resolve, transitioning to a more regenerative environment [8,12].

Maintaining an appropriate balance between pro-inflammatory and anti-inflammatory cytokines during the latency phase is essential for optimal DO outcomes. Excessive inflammation can lead to delayed healing or complications, while insufficient inflammation may impair the initiation of the regenerative process. Clinicians can monitor the inflammatory response during the latency phase through clinical assessment, laboratory markers, and imaging studies [12]. In cases of excessive inflammation, interventions such as adjusting the fixator tension, modifying the distraction protocol, or administering anti-inflammatory medications may be considered [12]. Understanding and managing the complex interplay of inflammatory mediators in this phase is crucial for optimizing the DO process and achieving successful outcomes in bone regeneration and lengthening procedures [8,12].

2.4. Distraction

The distraction phase follows soft callus formation by placing the osteotomized segment under constant tension. While the distractor settings vary, the soft callus is typically extended 1 mm per day and is broken into a rhythm of 0.25 mm every 6 hours [7,14]. The metabolically active soft callus is known as the fibrous interzone (FIZ) and is concentrated with fibroblasts, chondrocytes, and osteoblasts [12–14]. As osteoblasts mature 10–14 days following distraction, they produce bone matrix and create micro-column formation zones (MCFZ) along longitudinal collagen fibers [7,14]. The MCFZs serve as primary ossification centers, where intramembranous ossification occurs [20]. As the distractor separates the bone fragments in a calculated fashion, a fresh FIZ forms with MCFZs to deposit bone matrix parallel to the distraction force. Radiographic proof of bone mineralization becomes evident 7–10 days after distraction and should be monitored weekly to evaluate bone formation and distraction rate [14]. The distraction phase is complete when the desired bone length is achieved.

The distraction phase of DO does not mimic natural bone healing; rather, it ensures a persistent soft callus during lengthening. Much of this difference is attributed to the drastic change in signaling molecules. Primarily, the constant tension on the bone segments induces

constant IL-6 signaling, which slows osteoblasts from secreting osteoid [12]. Growth factors IGF-1 and FGF, along with BMP-2 and BMP-4, promote bone synthesis by recruiting more osteoblasts to the FIZ [7,12]. In addition to promoting osteoblast activity, osteoclast function is suppressed by elevated OPG levels.

2.5. Consolidation

The consolidation phase is dedicated to converting the woven bone in the FIZ to mature bone, revascularizing and reinnervating the lengthened segment, and re-establishing bone marrow [7,21]. Aside from the fixator remaining in place, this remodeling phase is similar to the final stage of bone healing. Primary bone is converted into Haversian bone with a large, central neurovascular supply [14]. As bone remodeling continues over 4–6 months, new bone marrow is also produced. While many of the inflammatory and bone formation signals decrease relative to the distraction phase, TGF- β 1 expression is maintained to promote bone mineralization. Osteoclasts play a major role in bone remodeling during this phase, and, as a result, there is higher expression of RANKL, IL-1, and TGF- β [12,21]. Consolidation occurs gradually over 4–6 months, and the remodeling is complete after 12–24 months [7,12].

3. Current Clinical Applications and Outcomes of Distraction Osteogenesis

Distraction osteogenesis has found wide-ranging clinical applications across various orthopedic and maxillofacial scenarios, demonstrating its versatility and efficacy in addressing a spectrum of conditions.

3.1. Correction of Extremity Length Discrepancies

One of the primary clinical applications of DO is in correcting limb length inequalities resulting from various etiologies such as congenital deformities, traumatic injuries, or post-surgical complications [5,15]. This can be performed either with traditional external fixators or through newer intramedullary lengthening nails which are discussed in more detail below. In 2023, a group of 41 patients with leg length discrepancy or limb deformity successfully underwent DO with two different distraction constructs and ended up with lengthening of 54.4 and 56.7 mm of lengthening, respectively, between the two groups [15]. More recently in 2024, DO was performed on a cohort of 58 patients with a median leg length discrepancy of 41 mm. Further, 9/58 patients in this cohort were treated with DO bilaterally for disproportionate short stature [5]. In the end, a median tibial distraction of 44 mm was achieved. Through controlled distraction, DO enables gradual bone lengthening, thereby restoring limb symmetry and function.

3.2. Management of Congenital Bone Deformities

DO plays a crucial role in correcting congenital bone deformities such as hip dysplasia, angular deformities, or skeletal dysplasia [22,23]. In one recent case report of an 11-year-old with untreated developmental dysplasia of the hip, a multi-staged DO was employed at the iliofemoral joint. Following treatment, the patient reported significant improvements in hip range of motion and quality of life [22]. In a larger recent study by Vogt et al., 45 patients underwent the simultaneous correction of angular deformity and limb-length discrepancy using distraction lengthening techniques [23]. Finally, in addition to limb lengthening unilaterally, DO has also proven useful for congenital short stature [24]. In one large study by Aldegheri et al., 160 patients with congenital short stature secondary to various genetic disorders were treated with DO. At the conclusion of the study, these patients showed an average lengthening of 7.8 cm (33% improvement) [24]. By utilizing the principles of bone regeneration, DO facilitates the gradual correction of deformities, leading to improved gait, skeletal alignment, and limb function.

3.3. Treatment of Large Bone Defects

In cases of significant bone loss secondary to trauma, infection, or tumor resection, DO offers a viable solution for reconstructing the skeletal defects. One major area where DO has been leveraged is in cases of nonunion or malunion, secondary to trauma or infection [4,16,25–27]. In one early study in 1994, Catagni et al. described a cohort of twenty-one hypertrophic nonunions, with a stable union achieved in all patients after a mean of 195 days [16]. Additionally, there was also a restoration of even leg lengths in 18/21 (86%) of patients who presented with leg length discrepancy [16]. In another study in 2017, Mahomed et al. followed a cohort of 33 patients who underwent distraction for nonunion. Following treatment, 29/33 (88%) were found to have union of the bone with an average time to union of 170 days [25]. Finally, a group at the Kalinga Institute of Medical Sciences in India in 2022 also successfully utilized DO for a series of 14 neglected femoral fractures, with an average time to healing of 176 days and an average improvement of knee flexion of nearly 60 degrees [26]. By promoting new bone formation through controlled distraction, DO aids in restoring bone continuity and function, thus avoiding the need for more invasive procedures like bone grafting or amputation.

3.4. Orthopedic Limb Salvage Procedures

DO serves as a valuable technique in limb salvage surgeries where preserving limb function is paramount, especially in cases involving extensive bone loss due to trauma or tumor resection. DO has been a longstanding tool for orthopedic oncologists repairing large bone defects following tumor removal. In fact, one of the earliest groups to describe this technique was Tsuchiya et al. in 1996 in 5 cases of Giant Cell Tumor of Bone [28]. This group then went on to employ this technique in a larger study of 19 patients with various oncologic indications in 1997 [29]. More recently, DO has even proven utility in limb salvage and revascularization efforts for patients with diabetic foot complications [30]. In 2022, Ou et al. described a cohort of 19 patients with Wagner Stage 4 diabetic foot ulcers who underwent transverse tibial bone transport followed by DO. This approach resulted in 18/19 (95%) wound healing rate and 18/19 (95%) limb salvage amongst the cohort [30]. This is especially notable given the difficulties that individuals with poorly controlled diabetes often incur with wound healing in addition to the high rates of amputation after reaching Stage 4 pathology. By promoting bone regeneration and preserving neurovascular structures, DO facilitates functional limb reconstruction while maintaining limb length and alignment.

3.5. Thumb Reconstruction

DO has shown promising outcomes in addressing thumb hypoplasia or deformities, particularly in cases classified as type IIIA. Through controlled distraction, DO enables the gradual lengthening and reshaping of the thumb, enhancing both esthetics and function [31,32]. One study by Upton et al. retrospectively reviewed 22 patients (41 thumbs) who had thumb malformation secondary to Apert syndrome over a 20-year period from 1999 to 2019. An average lengthening of 31.3 mm was achieved at the conclusion of treatment [32]. In addition, in many cases of DO of the digits, DO is used as an integral part of a two-step solution in which there is a lengthening component and a grafting component which is made to meet the lengthened component [31,33]. One study by Braga-Silva et al. documented 14 patients who underwent DO after distal phalanx amputation. Interestingly, once the distraction process had elongated the bone to a sufficient length, a nail graft was inserted distally with favorable cosmetic outcomes [31]. Finally, in another case report of a pediatric patient with multiple digit symbrachydactyly, a nonvascularized toe transfer was used in combination with DO to render a functional hand that was able to oppose finger and thumb [33]. By harnessing the principles of bone regeneration and controlled distraction, DO offers innovative solutions for challenging orthopedic conditions, ultimately improving patient outcomes, self-esteem, and quality of life.

4. Risks and Limitations

4.1. Prolonged Treatment Duration

One challenge of DO is the prolonged treatment duration and pre-operative planning required for bone distraction and consolidation. In addition to the desired final length and lengthening vector templating, surgeons must account for a patient's comorbidities [12]. For instance, older patients with multiple comorbidities may have slower ideal distraction rates due to less efficient wound healing when compared to the pediatric population. Once the distraction phase is complete, patients undergo an extended consolidation period, typically ranging from 4 to 6 months [7,12]. This prolonged duration contributes to extended immobilization, which leads to muscle atrophy and joint stiffening.

In addition to affecting surrounding joints and soft tissue, prolonged treatment duration is associated with extended discomfort and potential for infection. The hardware used in DO serves as a nidus for bacterial growth, posing a risk of infection that could invade the surrounding soft tissue, bone, and developing callus [34]. If an infection occurs, this only prolongs treatments and necessitates additional medical intervention.

4.2. Soft Tissue Complications

Soft tissue complications, such as pin tract infections and neuromuscular injuries, are common adverse events associated with external fixation devices used in DO [35]. Meticulous pin placement and care are crucial to decrease the risk of infections and damage to surrounding structures. As previously mentioned, pins are susceptible to infections, which could lead to cellulitis, abscess formation, and osteomyelitis [3,34]. Infection within the newly forming bone severely hinders bone union, rendering the DO process nearly ineffective [14]. The overall risk of infection of the superficial pin, tract, or deep tissue has been estimated to be approximately 5% [35]. Furthermore, pins can induce local inflammation around nerves and arteries, leading to bleeding, enhanced pain, or denervation [14].

Peripheral neuropathy is another common complication during the lengthening phase of DO. As the bone lengthens, increased tension is placed on surrounding nerves, occasionally leading to neuropathic symptoms such as paresthesia and numbness [12]. Similarly, surrounding muscles must adapt to the increased bone length, and it is especially challenging when the bone defect is associated with a congenital anomaly [3]. Domingos et al. reported that lengthening the bone more than 20% of its original length increases the risk of muscle contractures. These contractures, along with myalgias, complicate the recovery process, requiring extensive physical therapy and potentially long-term functional impairments.

4.3. Relapse and Improper Correction

Despite meticulous planning and execution, relapses and the improper correction of skeletal deformities can occur following DO procedures. When calculating the lengthening vector, it is crucial to consider the forces exerted by more robust surrounding muscles [14]. As they alter the gradual tension, bone deformities may arise, and biomechanics are disrupted [13,14]. This places the patient at an increased risk of additional corrective procedures. In addition to bone deformity, the newly formed bone may be increasingly fragile, especially in patients with a history of osteopenia or osteoporosis. These bones may easily fracture when the external frames are removed after consolidation or if excessive force is applied too early [2]. Finally, although rare, regression or shortening of the bone can occur following removal of fixators [36]. In a study by Mitsukawa et al., a patient experienced a 5 mm regression in the mandible after removal of the internal device.

4.4. Psychological Impact

The prolonged treatment duration and immobilization associated with DO can have a significant psychological impact on patients, particularly in pediatric populations [1,37–39]. During distraction, a bulky external fixator device must be kept on for a prolonged period of time. This makes these patients more susceptible to peer judgment as well as psychological complications [1,38]. One study by Wang et al. collected mental component score, physical

component score, and VAS pain scores both during and up to 2 years after undergoing DO for nonunion of the tibia. It was found that during treatment, the patients had reduced scores of physical and mental wellbeing as well as many patients reporting severe pain for long periods of time [39]. However, patient satisfaction and quality of life scores did improve significantly at the final follow-up after being treated with DO [39]. In another study by Liantis et al., it was reported that psychological distress was one of the top three major complications of DO in children and the top major complication of DO in adults [37]. Thus, it is important to communicate this to patients in order to set realistic expectations and maintain psychological health throughout the process. Psychological support and counseling may be necessary to address patient and caregiver concerns throughout the treatment process.

4.5. Cost and Resource Intensity

DO procedures can be resource-intensive and costly, requiring specialized equipment, prolonged hospital stays, and comprehensive post-operative care. In addition to close monitoring during the distraction phase, DO requires two intensive surgeries with general anesthesia to place and remove the fixators [13]. These surgeries require extensive planning, and proper resources and personnel should be available to handle complications [40]. Finally, undergoing DO is an expensive procedure for the patient and provider, and cost could affect the hardware in that region. As a result, access to skilled surgical teams and appropriate healthcare infrastructure may limit the widespread adoption of DO in certain settings.

4.6. Relative Contraindications

While there are not necessarily absolute contraindications, there are several patient populations who may not be considered ideal candidates for DO. First, while this process can be used in adult patients, its efficacy has been shown to be the greatest in children based on the robust biology of their bones [41,42]. In fact, research has shown that the rates of bone healing begin to slow as early as 20 years old [41,43]. Additionally, patients with diabetes may have corresponding wound healing issues which can hinder the efficacy of this mechanism [41,44,45]. Similarly, patients who are significant nicotine users may face wound healing issues and thus not be ideal candidates [41,46,47]. Finally, as is true with any form of bone healing but certainly DO, a patient's nutrition status must be optimized in order to ensure optimal outcomes, and thus patients who are severely malnourished may not be ideal candidates [41,48,49].

5. Future Directions and Conclusions

DO is an incredibly complex and intricate process that elegantly harnesses the body's natural tendency to heal while directing these forces in a way that offers real clinical solutions. However, as highlighted in the section above, this process in its current state has drawbacks and certainly has a great deal of room for advancement. Thus, researchers are constantly looking for new measures to promote more robust and rapid bone growth through the mechanism of DO while optimizing for time of treatment and preventing injury and complications as much as possible. Recent advancement efforts have aimed to improve the process of DO in two primary dimensions (Table 1). One area which this is occurring is in developments that can improve bone synthesis quality and modulate the speed at which bone is generated. The other realm of research development involves the distraction lengthener itself, including changes to the biomaterials involved in the structure as well as the structure of the device itself.

Table 1. Recent advancement efforts to improve the process of DO. Recent advancement efforts have aimed to improve the process of DO through various mechanisms approaching both the distraction device and the bone itself.

Mechanism	Innovation	Research Work
Bone Generation Improvement	Administration of BMPs, VEGF, and platelet-rich fibrin	Li et al., 2004 [34]
		Sabharwal et al., 2011 [17]
		Zhao et al., 2016 [50]
		Blatt et al., 2021 [51]
		Ou et al., 2022 [30]
		Rath et al., 2024 [52]
	Hyperbaric oxygen therapy	Sabharwal et al., 2011 [17] Zhao et al., 2016 [50]
	Low-intensity pulsed ultrasound, electromagnetic stimulation, platelet-rich plasma	Sabharwal et al., 2011 [17]
Device Improvement	MSC administration, cortical bone perforation	Zhao et al., 2016 [50] Ebrahimi et al., 2021 [53]
	Tissue engineering and regeneration	Farzin 2019 [54] Ebrahimi et al., 2021 [53] Farmani 2023 [55]
	Motorized IM nail	Safi et al., 2023 [15] Geiger et al., 2023 [18] Vogt et al., 2024 [5]
	Biodegradable distraction device/components	Zhao et al., 2016 [50]
	3D printed/custom distraction lengthener	Zhao et al., 2016 [50] Li et al., 2022 [11]

First, in the realm of bone generation, significant recent research has gone into the incorporation of external cytokines and growth factors that can be administered to the patient in order to supplement the bone's natural process [50]. As highlighted above, there are a number of inflammatory cytokines which are instrumental in the bone healing process and even exist in higher levels during DO than in physiologic conditions. The administration of BMPs, VEGF, and platelet-rich fibrin are three such factors which have been shown to aid in bone synthesis [17,30,34,50–52]. There are also several other strategies to assist bone synthesis which have been trialed with some degree of success, including MSC administration, cortical bone perforation, low-intensity pulsed ultrasound, electromagnetic stimulation, and hyperbaric oxygen therapy [17,50,53]. Finally, recent research has also been investigating various mechanisms of tissue engineering for bone regeneration in DO [53–55]. One example of this is guided bone regeneration (GBR) membranes which can be loaded or composed with various growth-promoting materials [53]. One such material which has been used in promoting growth in work by Ebrahimi et al. is metformin [53]. Additionally, in work by Farzin et al. and Farmani et al., novel strategies were developed in order to engineer a biocompatible scaffolding with the ultimate goal of promoting hard tissue generation, such as bone [54,55].

On the device side, there have also been developments in the materials used to make the distraction devices. One recent advancement which was touched on briefly above is the development of motorized intramedullary nails which act as distraction devices which are housed internally within the bone [5,15,18]. This development is especially exciting in that it helps to avoid many of the most common complications of DO discussed above [5,6,18]. By avoiding any external fixation devices, there is a lower chance of soft tissue complication in addition to a lesser psychosocial burden for patients with less visible hardware on their

body [15,18]. There has also been some research into the creation of using biomaterials to create a functional biodegradable distraction device. The idea behind this design is that these materials may be able to locally release some of the growth factors or other materials directly to the site of osteogenesis [50]. In addition, there has also been investigation into the possibility of using 3D printing technologies to custom print distraction lengtheners that are completely unique to the patient and the clinical indication [11,50].

DO has been commonly utilized in the field of oral and maxillofacial surgery for decades; however, in recent years, it has gained significant traction in the world of orthopedic surgery. Now, it is considered a highly feasible option to address a variety of orthopedic pathologies including limb length discrepancies following trauma, congenital limb deformities, and fracture malunions. Despite the advancements and promise behind DO, there are several limitations to the procedure, including a relatively high risk of complication, which cannot be overlooked. However, with recent advancements, researchers are developing promising solutions to the existing drawbacks of the procedure.

Author Contributions: Conceptualization, J.R.K.; Data Collection, B.A., M.G., C.F.W. and J.R.K.; Writing—Original Draft Preparation, B.A., M.G., C.F.W. and J.R.K.; Writing—Review and Editing, B.A., M.G., C.F.W. and J.R.K.; Supervision, J.R.K. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Sailhan, F. Bone lengthening (distraction osteogenesis): A literature review. *Osteoporos. Int.* **2011**, *22*, 2011–2015. [\[CrossRef\]](#) [\[PubMed\]](#)
2. Walter, A.; Domnic, M. Anatomical Concepts of Distraction Osteogenesis: An Orthopaedic Case in Western Kenya. *J. Orthop. Sports Med.* **2021**, *3*, 75–81. [\[CrossRef\]](#)
3. Cope, J.B.; Samchukov, M.L.; Cherkashin, A.M. Mandibular distraction osteogenesis: A historic perspective and future directions. *Am. J. Orthod. Dentofac. Orthop.* **1999**, *115*, 448–460. [\[CrossRef\]](#) [\[PubMed\]](#)
4. Rouse, B.J.; Sheridan, G.A.; Page, B.J.; Fragomen, A.T.; Rozbruch, S.R. Hypertrophic nonunion management with distraction osteogenesis: A scoping review of the literature. *OTA Int.* **2024**, *7*, e342. [\[CrossRef\]](#) [\[PubMed\]](#)
5. Vogt, B.; Lueckingsmeier, M.; Gosheger, G.; Laufer, A.; Toporowski, G.; Antfang, C.; Roedel, R.; Frommer, A. Magnetically driven antegrade intramedullary lengthening nails for tibial lengthening. *Bone Jt. J.* **2024**, *106-B*, 293–302. [\[CrossRef\]](#)
6. Tan, F.; Yang, C.; Zeng, J.; Li, J.; Li, P.; Qiao, Y.; Wang, J.; Zhang, J.; Xie, D.; Ye, S.; et al. A systematic review and meta-analysis: comparing the efficacy of the Ilizarov technique alone with lengthening over a nail for lower extremity bone defects. *BMC Musculoskelet. Disord.* **2024**, *25*, 699. [\[CrossRef\]](#)
7. Erverdi, N.; Motro, M. Principles of Distraction Osteogenesis. In *Alveolar Distraction Osteogenesis: ArchWise Appliance and Technique*; Erverdi, N., Motro, M., Eds.; Springer International Publishing: Cham, Switzerland, 2015; pp. 19–29. [\[CrossRef\]](#)
8. Adejuyigbe, B.; Kallini, J.; Chiou, D.; Kallini, J.R. Osteoporosis: Molecular Pathology, Diagnostics, and Therapeutics. *Int. J. Mol. Sci.* **2023**, *24*, 14583. [\[CrossRef\]](#)
9. Fink, B.; Pollnau, C.; Vogel, M.; Skripitz, R.; Enderle, A. Histomorphometry of distraction osteogenesis during experimental tibial lengthening. *J. Orthop. Trauma* **2003**, *17*, 113–118. [\[CrossRef\]](#)
10. Spiegelberg, B.; Parratt, T.; Dheerendra, S.; Khan, W.; Jennings, R.; Marsh, D.R. Ilizarov principles of deformity correction. *Ann. R. Coll. Surg. Engl.* **2010**, *92*, 101–105. [\[CrossRef\]](#)
11. Li, J.; Li, M.; Wang, W.; Li, B.; Liu, L. Evolution and Development of Ilizarov Technique in the Treatment of Infected Long Bone Nonunion with or without Bone Defects. *Orthop. Surg.* **2022**, *14*, 824–830. [\[CrossRef\]](#)
12. Compton, J.; Fragomen, A.; Rozbruch, S.R. Skeletal Repair in Distraction Osteogenesis: Mechanisms and Enhancements. *JBS Rev.* **2015**, *3*, e2. [\[CrossRef\]](#)
13. Natsu, S.S.; Ali, I.; Alam, S.; Giri, K.Y.; Agarwal, A.; Kulkarni, V.A. The biology of distraction osteogenesis for correction of mandibular and craniomaxillofacial defects: A review. *Dent. Res. J.* **2014**, *11*, 16–26.
14. Domingos, G.; Armés, H.; Dias, I.; Viegas, C.; Requiça, J. Distraction Osteogenesis: Biological Principles and Its Application in Companion Animals. In *Clinical Implementation of Bone Regeneration and Maintenance*; IntechOpen: London, UK, 2019. [\[CrossRef\]](#)
15. Safi, I.K.A.; Samadov, F.; Kanar, M.; Tuter, I.; Ozdemir, H.M. Deformity correction and limb lengthening with externally controlled motorized extendable intramedullary nails: Comparison of 2 different nails. *Acta Orthop. Traumatol. Turc.* **2023**, *57*, 169–175. [\[CrossRef\]](#)
16. Catagni, M.A.; Guerreschi, F.; Holman, J.A.; Cattaneo, R. Distraction osteogenesis in the treatment of stiff hypertrophic nonunions using the Ilizarov apparatus. *Clin. Orthop. Relat. Res.* **1994**, *301*, 159–163. [\[CrossRef\]](#)

17. Sabharwal, S. Enhancement of Bone Formation During Distraction Osteogenesis: Pediatric Applications. *JAAOS J. Am. Acad. Orthop. Surg.* **2011**, *19*, 101–111. [\[CrossRef\]](#) [\[PubMed\]](#)
18. Geiger, E.J.; Geffner, A.D.B.; Rozbruch, S.R.; Fragomen, A.T. Management of Segmental Tibial Bone Defects with the Magnetic Motorized Intramedullary Transport Nail: A Case Series. *J. Orthop. Trauma* **2023**, *37*, e459–e465. [\[CrossRef\]](#)
19. Black, S.R.; Kwon, M.S.; Cherkashin, A.M.; Samchukov, M.L.; Birch, J.G.; Jo, C.-H. Lengthening in Congenital Femoral Deficiency: A Comparison of Circular External Fixation and a Motorized Intramedullary Nail. *J. Bone Jt. Surg.* **2015**, *97*, 1432–1440. [\[CrossRef\]](#)
20. Brody-Camp, S.; Winters, R. Craniofacial Distraction Osteogenesis. In *StatPearls*; StatPearls Publishing: Treasure Island, FL, USA, 2023. Available online: <http://www.ncbi.nlm.nih.gov/books/NBK560915/> (accessed on 17 January 2024).
21. Yang, S.; Wang, N.; Ma, Y.; Guo, S.; Guo, S.; Sun, H. Immunomodulatory effects and mechanisms of distraction osteogenesis. *Int. J. Oral Sci.* **2022**, *14*, 4. [\[CrossRef\]](#)
22. Amin, O.A.; AlAmoudi, S.; Amin, B.A.; Alamoudi, A. Neglected Developmental Hip Dysplasia Treated with External Iliofemoral Distraction, Open Reduction, and Pelvic Osteotomy: Eleven-Year Follow-Up. *J. Am. Acad. Orthop. Surg. Glob. Res. Rev.* **2024**, *8*, e23.00291. [\[CrossRef\]](#)
23. Vogt, B.; Biermann, C.; Gosheger, G.; Laufer, A.; Rachbauer, A.; Antfang, C.; Lueckingsmeier, M.; Toporowski, G.; Tretow, H.; Roedl, R.; et al. Simultaneous correction of leg length discrepancy and angular deformity of the distal femur with retrograde Precice nails: A retrospective analysis of 45 patients. *Acta Orthop.* **2024**, *95*, 364–372. [\[CrossRef\]](#)
24. Aldegheri, R. Distraction osteogenesis for lengthening of the tibia in patients who have limb-length discrepancy or short stature. *J. Bone Jt. Surg.* **1999**, *81*, 624–634. [\[CrossRef\]](#)
25. Mahomed, N.; O'Farrell, P.; Barnard, A.-C.; Birkholtz, F.F. Monofocal Distraction Treatment of Stiff Aseptic Tibial Nonunions with Hexapod Circular External Fixation. *J. Limb Lengthening Reconstr.* **2017**, *3*, 101–106. Available online: https://journals.lww.com/jllr/fulltext/2017/03020/monofocal_distraction_treatment_of_stiff_aseptic.7.aspx (accessed on 23 July 2024).
26. Srikant, K.; Soni, A.; Pradhan, S.; Gulia, A.; Sandeep, B.; Kafley, R.; Venkatesan, V.; Sayashi, S.; A Mohanty, S.; Mohanty, S.A.; et al. Ilizarov Fixator-Assisted Management of Neglected Femur Fractures by Open Intramedullary Nailing: A Case Series. *Cureus* **2023**, *15*, e50864. [\[CrossRef\]](#) [\[PubMed\]](#)
27. Nicholson, J.; Makaram, N.; Simpson, A.; Keating, J. Fracture nonunion in long bones: A literature review of risk factors and surgical management. *Injury* **2020**, *52*, S3–S11. [\[CrossRef\]](#) [\[PubMed\]](#)
28. Tsuchiya, H.; Tomita, K.; Shinokawa, Y.; Minematsu, K.; Katsuo, S.; Taki, J. The Ilizarov method in the management of giant-cell tumours of the proximal tibia. *J. Bone Joint Surg. Br.* **1996**, *78*, 264–269. [\[CrossRef\]](#)
29. Tsuchiya, H.; Tomita, K.; Minematsu, K.; Mori, Y.; Asada, N.; Kitano, S.; Nicol, S.; Jackson, M.; Monsell, F.; Hilven, P.H.; et al. Limb salvage using distraction osteogenesis. A classification of the technique. *J. Bone Jt. Surg.* **1997**, *79*, 403–411. [\[CrossRef\]](#)
30. Ou, S.; Xu, C.; Yang, Y.; Chen, Y.; Li, W.; Lu, H.; Li, G.; Sun, H.; Qi, Y. Transverse Tibial Bone Transport Enhances Distraction Osteogenesis and Vascularization in the Treatment of Diabetic Foot. *Orthop. Surg.* **2022**, *14*, 2170–2179. [\[CrossRef\]](#)
31. Braga-Silva, J.; Padoin, A.V. Distraction osteogenesis and free nail graft after distal phalanx amputation. *J. Hand Surg.* **2012**, *37*, 2541–2546. [\[CrossRef\]](#)
32. Upton, J.I.; McNamara, C.T.B.; Ali, B.; Nuzzi, L.C.B.; Taghinia, A.H.M.; Labow, B.I. Distraction Lengthening of the Apert Thumb. *Plast. Reconstr. Surg.* **2022**, *149*, 691e–699e. [\[CrossRef\]](#)
33. Netscher, D.T.; Lewis, E.V. Technique of nonvascularized toe phalangeal transfer and distraction lengthening in the treatment of multiple digit symbrachydactyly. *Tech. Hand Up. Extremity Surg.* **2008**, *12*, 114–120. [\[CrossRef\]](#)
34. Li, G. New developments and insights learned from distraction osteogenesis. *Curr. Orthop. Pr.* **2004**, *15*, 325–330. [\[CrossRef\]](#)
35. Li, Y.; Pan, Q.; Xu, J.; He, X.; Li, H.A.; Oldridge, D.A.; Li, G.; Qin, L. Overview of methods for enhancing bone regeneration in distraction osteogenesis: Potential roles of biomaterials. *J. Orthop. Transl.* **2021**, *27*, 110–118. [\[CrossRef\]](#)
36. Mitsukawa, N.; Satoh, K.; Morishita, T.; Hosaka, Y. Clinical Application of Distraction Osteogenesis for Traumatic Maxillofacial Deformities. *J. Craniofacial Surg.* **2006**, *17*, 431. [\[CrossRef\]](#) [\[PubMed\]](#)
37. Liantis, P.; Mavrogenis, A.F.; Stavropoulos, N.A.; Kanellopoulos, A.D.; Papagelopoulos, P.J.; Soucacos, P.N.; Babis, G.C. Risk factors for and complications of distraction osteogenesis. *Eur. J. Orthop. Surg. Traumatol.* **2013**, *24*, 693–698. [\[CrossRef\]](#) [\[PubMed\]](#)
38. Paley, D. Problems, obstacles, and complications of limb lengthening by the Ilizarov technique. *Clin. Orthop. Relat. Res.* **1990**, *250*, 81–104. [\[CrossRef\]](#)
39. Wang, H.; Wei, X.; Liu, P.; Fu, Y.-H.; Wang, P.-F.; Cong, Y.-X.; Zhang, B.-F.; Li, Z.; Lei, J.-L.; Zhang, K.; et al. Quality of life and complications at the different stages of bone transport for treatment infected nonunion of the tibia. *Medicine* **2017**, *96*, e8569. [\[CrossRef\]](#)
40. D'Agostino, E.; Calnan, D.R.; Whitson, W.; Stotland, M.; Bauer, D.F. The Use of Distraction Osteogenesis in the Treatment of Rickets-Associated Craniosynostosis. *World Neurosurg.* **2019**, *131*, 200–206. [\[CrossRef\]](#)
41. Alzahrani, M.M.; Anam, E.; AlQahtani, S.M.; Makhdom, A.M.; Hamdy, R.C.; Alzahrani, M.M.; Anam, E.; AlQahtani, S.M.; Makhdom, A.M.; Hamdy, R.C. Strategies of enhancing bone regenerate formation in distraction osteogenesis. *Connect. Tissue Res.* **2017**, *59*, 1–11. [\[CrossRef\]](#)
42. Borgiani, E.; Figge, C.; Kruck, B.; Willie, B.M.; Duda, G.N.; Checa, S. Age-Related Changes in the Mechanical Regulation of Bone Healing Are Explained by Altered Cellular Mechanoreponse. *J. Bone Miner. Res.* **2019**, *34*, 1923–1937. [\[CrossRef\]](#)
43. Fischgrund, J.; Paley, D.; Suter, C. Variables affecting time to bone healing during limb lengthening. *Clin. Orthop. Relat. Res.* **1994**, *301*, 31–37. [\[CrossRef\]](#)

44. Thrailkill, K.M.; Liu, L.; Wahl, E.C.; Bunn, R.C.; Perrien, D.S.; Cockrell, G.E.; Skinner, R.A.; Hogue, W.R.; Carver, A.A.; Fowlkes, J.L.; et al. Bone formation is impaired in a model of type 1 diabetes. *Diabetes* **2005**, *54*, 2875–2881. [[CrossRef](#)]
45. Jiao, H.; Xiao, E.; Graves, D.T. Diabetes and Its Effect on Bone and Fracture Healing. *Curr. Osteoporos. Rep.* **2015**, *13*, 327–335. [[CrossRef](#)] [[PubMed](#)]
46. Ma, L.; Zheng, L.W.; Sham, M.H.; Cheung, L.K. Uncoupled angiogenesis and osteogenesis in nicotine-compromised bone healing. *J. Bone Miner. Res.* **2010**, *25*, 1305–1313. [[CrossRef](#)] [[PubMed](#)]
47. Patel, R.A.; Wilson, R.F.; Patel, P.A.; Palmer, R.M. The effect of smoking on bone healing: A systematic review. *Bone Jt. Res.* **2013**, *2*, 102–111. [[CrossRef](#)] [[PubMed](#)]
48. Choi, I.H.; Chung, C.Y.; Cho, T.J.; Yoo, W.J. Angiogenesis and mineralization during distraction osteogenesis. *J. Korean Med. Sci.* **2002**, *17*, 435–447. [[CrossRef](#)]
49. Lumpkin, C.K.D.; Aronson, J.; Shen, X.C.; Gao, G.G.; Skinner, R.A.; Badger, T.M. The impact of total enteral nutrition on distraction osteogenesis in a rat model. *J. Bone Miner. Res.* **1996**, *11*, 962–969. [[CrossRef](#)]
50. Zhao, D.; Wang, Y.; Han, D. Periosteal Distraction Osteogenesis: An Effective Method for Bone Regeneration. *BioMed Res. Int.* **2016**, *2016*, 2075317. [[CrossRef](#)]
51. Blatt, S.; Thiem, D.G.E.; Kyyak, S.; Pabst, A.; Al-Nawas, B.; Kämmerer, P.W. Possible Implications for Improved Osteogenesis? The Combination of Platelet-Rich Fibrin with Different Bone Substitute Materials. *Front. Bioeng. Biotechnol.* **2021**, *9*, 640053. [[CrossRef](#)]
52. Rath, P.; Mandal, S.; Das, P.; Sahoo, S.N.; Mandal, S.; Ghosh, D.; Nandi, S.K.; Roy, M. Effects of the multiscale porosity of decellularized platelet-rich fibrin-loaded zinc-doped magnesium phosphate scaffolds in bone regeneration. *J. Mater. Chem. B* **2024**, *12*, 5869–5883. [[CrossRef](#)]
53. Ebrahimi, L.; Farzin, A.; Ghasemi, Y.; Alizadeh, A.; Goodarzi, A.; Basiri, A.; Zahiri, M.; Monabati, A.; Ai, J. Metformin-Loaded PCL/PVA Fibrous Scaffold Preseeded with Human Endometrial Stem Cells for Effective Guided Bone Regeneration Membranes. *ACS Biomater. Sci. Eng.* **2021**, *7*, 222–231. [[CrossRef](#)]
54. Farzin, A.; Hassan, S.; Ebrahimi-Barough, S.; Ai, A.; Hasanzadeh, E.; Goodarzi, A.; Ai, J. A facile two step heat treatment strategy for development of bioceramic scaffolds for hard tissue engineering applications. *Mater. Sci. Eng. C* **2019**, *105*, 110009. [[CrossRef](#)]
55. Farmani, A.R.; Nekoofar, M.H.; Ebrahimi-Barough, S.; Azami, M.; Najafipour, S.; Moradpanah, S.; Ai, J. Preparation and In Vitro Osteogenic Evaluation of Biomimetic Hybrid Nanocomposite Scaffolds Based on Gelatin/Plasma Rich in Growth Factors (PRGF) and Lithium-Doped 45s5 Bioactive Glass Nanoparticles. *J. Polym. Environ.* **2023**, *31*, 870–885. [[CrossRef](#)]

Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.