"Distraction Osteogenesis in Orthodontics: A Comprehensive Review

¹Dr. Viraj Shyam Ingale; ²Dr. Chetan Patil; ³Dr. Pradeep Kawale; ⁴Dr. Pradeep Kumar; ⁵Dr. Snehal Bhalerao; ⁶Dr. Ben Joshua; ⁷Dr. Aameer Parkar; ⁸Dr. Sachin Philip

Abstract:- Distraction osteogenesis (DO) has emerged as a revolutionary technique in the field of orthopaedic surgery, offering solutions for limb lengthening, bone deformity correction, and craniofacial reconstruction. This article provides a comprehensive overview of the principles, techniques, and advancements in distraction osteogenesis, highlighting its applications, challenges, and future directions. From historical perspectives to contemporary innovations, this review aims to elucidate the evolution of DO and its impact on patient outcomes.Some of the downsides of DO include incorrect vector alignment, which results in unfavourable loading of joints and tissues, scarring, pain, dental hygiene visits activation. daily for maintenance, and Orthodontists, with their expertise in biomechanics and long-term patient care, are ideally positioned to administer and integrate this innovative therapeutic treatment.

Keywords:- Distraction Osteogenesis, Orthodontics, Bone Deformity, Surgical Techniques, Therapeutic Treatment, Complications.

I. INTRODUCTION

Intraoral Distraction Osteogenesis (DO Callus Distraction Histogenesis (DH) is an orthopaedic/surgical process that lengthens or reshapes bones and associated soft tissues of the stomatognathic system by controlled traction of separated bone segments, resulting in the formation of new bone and adjacent soft tissue. These processes are based on the fundamental biological concepts of osteogenesis and histology. It is frequently used to address irregularities or deformities in the jaw or other facial bones that may impair the function or look of the face [1, 2]. Distraction Osteogenesis dates back to Hippocrates, Codivilla (1905), and GravrilAIIlizorov (limb lengthening)^[3, 4]. McCarthy et colleagues. introduced distraction osteogenesis to the human jaw for the first time in 1992^{. [1, 5]}Liou and Huang ^[6, 7] first used DO in orthodontic treatment in 1998, utilizing a technique known as " Dental distraction" to rapidly retract canines. Iseri et al. and Kisnisci et al. later devised a separate procedure known as "dentoalveolar distraction" for quick canine distalization by osteotomies [8, 9]. Intraoral DO can be an effective treatment for a variety of conditions, including congenital and acquired abnormalities of the jaw, midface, zygomatic bones, and calvarium, condylar reconstruction in temporomandibular joint ankylosis, facial injuries including non-healing fractures, cystic and oncologist jaw deformities, and issues resulting from

previous surgery. Cases of syndromic (Pierre-Robin, Godenhar, Treacher Collins, Facial Clefts, Alveolar Clefts, Cranial Microsomia) or calvarial, fronto-orbital complex hypoplasias, and non-syndromic bimaxillary shortening, such as a retrognathic mandible in Obstructive Sleep Apnea (OSA) where orthognathic surgery is not the first choice, are indicated for DO. It can also be used to repair bite or dental abnormalities, such as an overbite or underbite, tooth movement (e.g., canine), impacted teeth, or a group of teeth (e.g., anterior teeth retraction and palate expansion). DO treatment includes the correction of alveolar atrophies, cross biting, and occlusal plane canting. DO has been demonstrated to be useful in reducing orthodontic treatment time ^[10] DO/DH operations have an advantage over normal orthodontic and orthognathic procedures since there is no relapse caused by soft tissue histogenesis and development [11, 12]. DO/DH treatments in neonates for mandibular advancement for airway expansion due to development difficulties can prevent tracheostomy ^[13, 14]. DO can shorten treatment duration and minimize difficulties in future orthodontic and orthognathic surgeries ^[15, 16]. Some of the downsides of DO include incorrect vector alignment, which results in unfavourable loading of joints and tissues, scarring, pain, dental hygiene maintenance, and daily visits for activation. Such disadvantages are mitigated by developments in three-dimensional control device designs, resulting in greater accuracy and less deleterious influence on neighbouring tissue [17, 18].

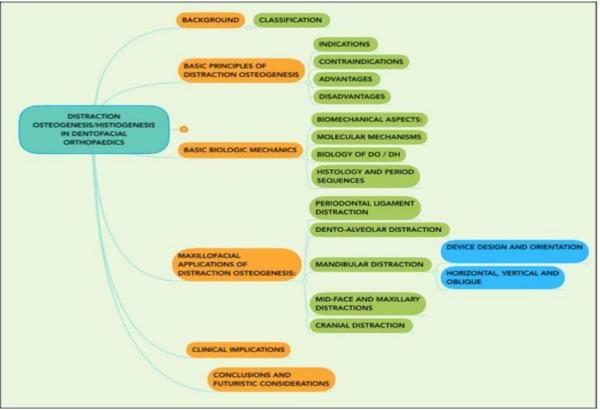


Fig. 1: Brief Outline of Distraction Osteogenesis

II. DEVICE

A distractor is a device made up of two pieces joined by a screw and fastened to the bones/teeth to be distracted. Distraction of segments occurs over a period of several weeks with screw activation. Distractor devices used in the maxillofacial region can be classified according to their location, such as mandibular, midface or maxillary, alveolar, or transport (neo-mandible/neocondyle reconstruction). Devices can also be classified according to their application, such as (RED) Rigid External Distractors, which are anchored to the bone using percutaneous pins, fixation clamps, and distraction rods, and Internal Distractors, which can be implanted under or above the oral mucosa. External distractors can further be divided into unidirectional, bidirectional and multiplanner, whereas internal distractors can be mandibular intraoral distractors, modular internal distractors (MID) and tooth borne distractors. Devices can be classed as tooth-borne, bone-borne, or hybrid ^{[19].} The distraction device's material can also be used to classify it, with bioresorbable devices employed in infants with congenital abnormalities and non-resorbable metallic devices. Distraction techniques can also be classified into two types: callotasis and distraction of the bone development plate, which results in epiphysiolysis and chondrodiatasis. Distraction strategies can be classified into three types: monofocal, bifocal, and trifocal. They are classified based on the amount of osteodistraction gaps and calluses caused by surgical fracture, with monofocals utilized for modest corrections and trifocals used for large surgical realignments ^{[20, 21].}

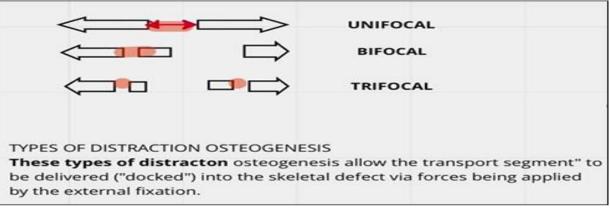


Fig. 2: Types of Distraction Osteogenesis

III. BASIC PRINCIPLES

The appliance's position on the mandible/maxilla is determined by a number of factors, including the biological and mechanical forces that shape the regenerate (new bone formed during the active period of distraction osteogenesis) and the desired change in shape and function [1, 22].Both biologic and mechanical forces must meet the orthodontic treatment goals of structural integrity, functional optimization, and aesthetics. Force transduction via nearby structures modulates tissue regeneration between bone fragments by altering the stress generated within the callus [22, 23]. Stable fixation of the osteomised bone segments is important for successful distraction, and the distraction axis must be parallel to the bone's anatomic axis rather than the biomechanical axis of loading to avoid undesirable joint loading. Clinical studies have confirmed that the device's orientation to the mandible has a direct influence on skeletal morphology, and the best approach to describe the device's position is in relation to the mandibular body's long axis. There are three different forms of device placement: vertical, horizontal, and oblique. During planning distraction, the significant impact of biological and mechanical force systems must be considered in order to predict their consequences. The velocity and rhythm of the separation pressures influence the success of new bone formation throughout the distraction process [24, 25]. The stages of distraction osteogenesis are presented in the following order:

A. Osteotomy

To start and maintain the distraction osteogenesis, each bone segment that has undergone an osteotomy must have a enough number of live osteocytes. Because the periosteum in the well-vascularized craniofacial region affords significant osteoblastic activity, complete osteotomy is not preferable over corticotomy^{[26].}

B. Latency

Soft calluses are formed during the latency phase of distraction osteogenesis, which follows a histology pattern similar to bone mending. The recommended first delay time ranges from 5 to 10 days ^{[27].}

C. Distraction

During this time, applying progressive tension to the soft callus interferes with the fracture's natural healing process. The tension caused by this traction force creates a dynamic microenvironment that encourages the formation of new tissue in a direction perpendicular to the traction vector. During distraction, four zones emerge: a fibrous, less vascular centre with collagen fibres parallel to the distraction vector, a transition zone of early bone production, a bone remodelling zone, and mature bone at the ends. The distraction process normally progresses by 0.5 to 1 mm per day ^{[1, 28].}

REMODELING AND CONSOLIDATION

Bone maturation initiates once the newly formed bony tissue begins to resemble preexisting bone and undergoes soft tissue adaptation, continuing for a year or longer. Following cessation of distraction, the softened callus solidifies, predominantly through intramembranous ossification, completely filling the gap with woven bone. Paediatric patients are advised to undergo a 3-5 week phase, while adults should consider a 6-12 week phase for craniofacial bone distraction ^[29].

Distraction osteogenesis encompasses a four-stage process involving a fibrous central zone, transition zone, remodelling zone, and mature zone. During the fibrous central stage, mesenchymal proliferation occurs with longitudinally oriented collagen bundles. The transition stage witnesses the formation of osteoids along these bundles. Remodelling occurs in the subsequent phase, involving osteoclast formation and restructuring of the nascent bone. The final stage, the mature zone, marks the conversion of mechanical forces into cellular signals through mechanical transduction ^{[30].}

Distinctive aspects of the healing process in distraction osteogenesis compared to fracture repair include regulated microtrauma and an intramembranous ossification mechanism, diverging from the endochondral ossification seen in fracture healing ^{[1, 26].}

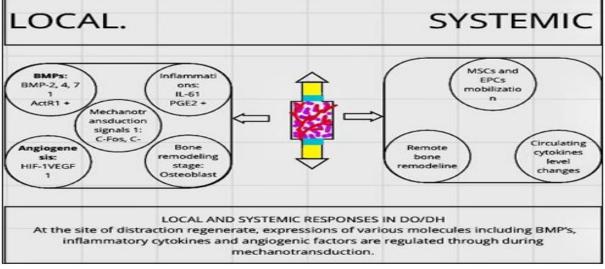


Fig. 3: Local and Systemic Responses in DO/DH

IV. MOLECULAR MECHANISM

The Distraction Osteogenesis/Distraction Histogenesis (DO/DH) technique harnesses the regenerative potential of musculoskeletal tissues, triggering various regulatory processes. Research utilizing next-generation sequencing, proteomics, and metabolomics is uncovering the molecular pathways involved in DO/DH. Tension stress during DO/DH impacts signal transduction molecules, BMPs, inflammatory and vascular proteins, and epigenetic factors, with ongoing exploration to enhance clinical applications. During DH, inflammatory and immunomodulatory reactions are pivotal for bone homeostasis, with high levels of tensile strain inducing the expression of pro-inflammatory genes like Prostaglandins and COX2. Bone remodelling, essential for medullary cavity recanalization during late consolidation in DO, can be regulated by PEMF, ultrasound, and shock wave therapies. Mechanotransductionsignalling mechanisms such as YAP, TAZ, and ERK-1/2 stimulate genes responsible for

bone homeostasis and regeneration, highlighting the interconnectedness of mechanical stimuli, gene activation, and chemical response at molecular and cellular levels. The DH process relies on the production of Endothelial Progenitor Cells (EPCs) and their homing to the site of new bone production. Activation of VEGF receptors 1 and 2 is crucial for neovascularization and bone production during DO. Hypoxia-induced factor 1 and mechanical manipulation during consolidation influence the paracrine loop of VEGF and BMP-2, maintaining the coupling of angiogenesis and osteogenesis. Transportation of bone marrow and adiposederived MSCs has been shown to expedite bone consolidation in DO and DH models, with growth hormones and EP2-specific agonists investigated for improving bone regeneration. Post-transcriptional regulation of DO/DHrelated genes relies heavily on small non-coding RNAs (mRNAs), and various scaffolding materials are under to promote bone investigation development and consolidation.

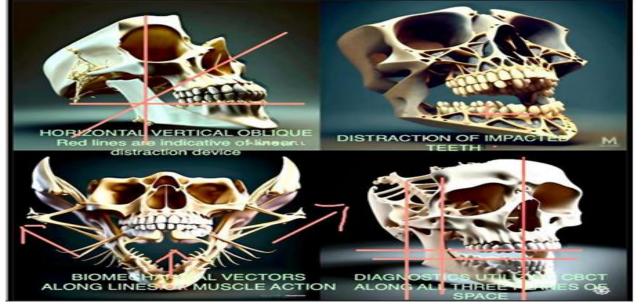


Fig. 4: Clinical Applications

V. CLINICAL IMPLICATIONS FOR MAXILLOFACIAL APPLICATIONS OF DISTRACTION OSTEOGENESIS

Clinical implications for maxillofacial applications of distraction osteogenesis revolve around device design, configuration, sturdiness, and attachment stability, all of which significantly impact procedural success. Factors such as distraction device orientation, operational vector alignment with anatomical axes, bone geometric morphometrics, cross-sectional area, density, transport-gap length, and soft tissue tension influence the quality of tissue generated.

Choice between external and internal devices is a key planning factor. External devices offer three-dimensional transportation capability and optimal vector generation but may result in facial scarring and increased distance between force points, with limited ability to alter force direction postinsertion. Internal devices, though smaller, overcome these drawbacks, enabling occlusal adjustments and micromanagement during distraction. Paediatric patients typically avoid external devices unless airway concerns arise.

In patients with active growth, distraction procedures are deferred until growth maturity due to bone elasticity. Osseodistraction with corticotomy of the external cortex is advised in younger individuals. Adults, with a more resistant internal cortex, exhibit reduced failure risks. A latency period of 4–7 days post-osteotomy precedes distraction, with premature bone union more likely if delayed beyond 10 to 14 days. The gold standards for craniofacial distraction osteogenesis include a distraction rate of 1mm/day and a delay of 5 to 7 days.

Recent maxillofacial procedures involving distraction osteogenesis, often conducted collaboratively with orthodontists, adhere to these principles to achieve optimal outcomes.

VI. DENTO-ALVEOLAR DISTRACTION

Chin and Toth ^[45] introduced vertical mandibular alveolar distraction osteogenesis to clinical practice in 1996. Block et al. validated distraction osteogenesis for alveolar ridge augmentation in the mandibular canine. Osteodistraction of the alveolar process is more effective for three-dimensional reconstruction than grafting or tissue regeneration. Alveolar ridge distraction is advised to improve bone volume for implant insertion and orthodontic tooth movement.

VII. MANDIBULAR DISTRACTION

Snyder et al. verified the clinical application of Ilizarov's bone lengthening principles for facial and jaw areas, employing an external distractor for canine distraction. McCarthy et al. and Guerrero utilized external distractors for treating congenital facial defects and midsymphyseal widening with a hyrax-type screw, respectively. These techniques were applied in patients with facial dysmorphism, respiratory issues, and conditions such as Pierre Robin syndrome, Treacher Collins syndrome, micrognathia, and craniofacial microsomia. They were also used for managing temporomandibular joint ankylosis and post-ablative mandibular problems, as well as infant or paediatric patients with sleep apnea or swallowing difficulties.

Placement of intraoral or external devices involves trans-cutaneous (submandibular) or intraoral incisions. Comparison of distraction-based osteotomies to conventional ones shows advantages such as earlier surgery, shorter procedures, fewer postoperative complications (including transfusions), and reduced need for additional surgeries (such as grafts). Additionally, the lengthening or expansion of muscles and soft tissue above (distraction histogenesis) over time leads to decreased relapse rates.

A. Periodontal ligament distraction

In 1998, Liou and Huang identified osteogenesis in the periodontal ligament during rapid orthodontic tooth movement, which is similar to osteogenesis in the mid-palatal suture during rapid palatal expansion. Distractor activation at 1mm/day, along with interseptal bone fracture of the extraction socket, has been shown to shorten orthodontic treatment time by 3-4 months ^{[50, 51].}

VIII. MAXILLOFACIAL AND MID FACE APPLICATIONS

In one of the early clinical trials, Polley et al. used a fixed cranial halo to distract the midface. The benefits and drawbacks of Rigid External Distraction (RED) are the same as those outlined in other distraction treatments. Figueroa et al. exhibited complete clinical regeneration of hard and soft tissues in the midface with distraction. Maxillary Le Fort I distraction is recommended for retrusion/protrusion in patients with Cleft Lip and Palate who have associated dental and soft tissue issues. Other indications for Midfacial Distraction with Maxillary Le Fort III distraction for midface retrusion include respiratory issues, malocclusion,

and severe dysphmorphism, especially in syndromic craniofacial synostosis with exorbitism and cranial microsomia (can be treated with combined maxilla-mandibular distraction). ^[52]

IX. CRANIAL DISTRACTION

In one of the early clinical trials, Polley et al. used a fixed cranial halo to distract the midface. The benefits and drawbacks of Rigid External Distraction (RED) are the same as those outlined in other distraction treatments. Figueroa et al. exhibited complete clinical regeneration of hard and soft tissues in the midface with distraction. Maxillary Le Fort I distraction is recommended for retrusion/protrusion in patients with Cleft Lip and Palate who have associated dental and soft tissue issues. Other indications for Midfacial Distraction with Maxillary Le Fort III distraction for midface retrusion include respiratory issues, malocclusion, and severe dysphmorphism, especially in syndromic craniofacial synostosis with exorbitism and cranial microsomia (can be treated with combined maxilla-mandibular distraction). ^[52]

X. ORTHODONTIC TREATMENT PROTOCOL

- Pre-distraction orthodontic treatment encompasses tasks such as levelling, alignment, coordination of maxillary and mandibular arches, and decompensation. This involves positioning teeth over the basal arch and inducing root divergence at the osteotomy site to facilitate subsequent procedures.
- Orthodontic interventions during the distraction and consolidation phases involve the use of intramaxillary and/or intermaxillary elastics, mini implants, and headgear to initiate movement towards the post-distraction position. These measures also aid in controlling clockwise or counterclockwise rotation of distracted segments based on evolving clinical needs. Orthodontic adjustments during this stage provide three-dimensional control in the horizontal, vertical, and transverse dimensions, establishing an optimal biomechanical system for correcting distracted segments.
- Post-distraction orthodontic care focuses on finalizing residual dentoalveolar movements, refining occlusion, aligning roots, and artistically positioning teeth to achieve functional occlusion and desirable facial aesthetics.
- Retention of the achieved dentoalveolar and bone shape and position is achieved through the use of fixed or removable retainers.



Fig. 5: Extrusion of Impacted Teeth

Experimental studies have shown that after four days of consolidation, the load-bearing group exhibited a higher percentage of regenerated bone and elevated levels of osteocalcin, type I collagen, and morphogenetic proteins 2 and 4 (BMP-2 and BMP-4). Various extracellular matrix (ECM) proteins, cytokines, and growth factors play essential roles in bone formation processes at the distraction gap. According to Okazaki et al., recombinant human fibroblast growth factor (FGF) was utilized towards the end of the distraction period. The effectiveness of distraction osteogenesis (DO) has been underscored by ECM proteins like osteocalcin, whose mRNA and protein expressions vary throughout the distraction phases. These regulatory factors experience changes in mRNA and protein expressions during distraction stages, emphasizing the importance of timing the administration of specific proteins for optimal results.

Protecting the main sources of osteoblast precursors, namely the periosteum and endosteum, from heat or mechanical damage during surgery is crucial for successful osteogenesis. Adequate blood supply to the distraction site is essential for osteogenesis, necessitating careful attention to ensure proper vascularization of the soft tissues near the potential distraction site. Arterial insufficiency during regeneration may lead to ischemic fibrogenesis, resulting in an irregular collagen network rather than the desired dense, uniform collagen pattern. Cystic degeneration in the regeneration process has been associated with venous outflow restriction.

During corticotomy, it is imperative to perform the procedure through a small periosteal aperture, as early investigations in long bones have highlighted the importance of preserving an intact periosteum and endosteum for effective osteogenesis.

XI. CONCLUSIONS AND FUTURISTIC CONSIDERATIONS

Orthodontists, with their expertise in biomechanics and long-term patient care, are ideally positioned to administer and integrate this innovative therapeutic treatment. As distraction osteogenesis gains more clinical recognition, it will be imperative for orthodontists to grasp the next generation of internal distraction devices and incorporate distraction osteogenesis into their treatment plans.

Similar to other orthognathic surgeries, distraction osteogenesis relies on the collaboration and preparation of both the surgeon and orthodontist. While distraction osteogenesis is a critical clinical process for lengthening mandibles and other craniofacial bones, it requires interdisciplinary and coordinated care to ensure a positive clinical outcome for the patient.

The future of distraction osteogenesis/distraction histogenesis (DO/DH) holds promise in managing osteoarthritis (OA) by unloading joint cartilage, reducing inflammatory infiltrates and pain, and promoting angiogenesis and function. Internal distractors can mitigate Research in DO/DH is expected to expand our understanding of tissue regeneration, including neural regeneration in vascular and neurological disorders. While DH traditionally employs minimally invasive approaches like ultrasound and electromagnetic stimulation, current methods, such as local transport of undifferentiated cells and mechanotransduction-induced molecules, as well as hormone injections, are poised to enhance bone growth and favor distraction procedures for improved clinical outcomes.

Ongoing research in these areas aims to further our understanding of basic biological processes, laying the groundwork for enhanced therapeutic applications of the DH approach.

- Acknowledgement: Nil.
- Conflict of Interest: Nil.
- Financial Support: Nil.

REFERENCES

- [1]. Natu SS, et al. The biology of distraction osteogenesis for correction of mandibular and craniomaxillofacial defects: A review: Dental research journal (Isfahan). 2014 Jan Feb;11(1):16-26.
- [2]. Menon S, et al. Distraction Osteogenesis in management of mandibular deformities: Med J Armed Forces India. 2005 oct;61(4):345-347.
- [3]. Birch JG. A brief history of limb lengthening: J Pediatrorthop. 2017 sep;37(suppl 2):S1-S8.
- [4]. Spiegelberg B, et al. Ilizarov principles of deformity correction. Ann R CollSurg Engl. 2010 Mar;92(2):101 105.
- [5]. Neelakandan RS, Darpan Bhargava. Transport Distraction Osteogenesis for maxillomandibular reconstruction: Current concepts and applications. J. Maxillofac oral surg. 2012 Sep; 11(3):291-299.
- [6]. Iseri H, et al. Rapid canine retraction and orthodontic treatment with dentoalveolar distraction osteogenesis. Am J OrthodDentofacialOrthop. 2005 May; 127(5):533 41.
- [7]. Koteswara Prasad NK. et al. Rapid maxillary canine retraction by dental distraction : A clinical study. Natl J Maxillofac Surg. 2014 Jan-Jun;5(1):6-13.
- [8]. Kateel SK, et al. A comparative study of canine retraction by distraction of the periodontal ligament and dentoalveolar distraction methods. J Maxillofac oral surg. 2016 Jun;15(2):144-145.
- [9]. Kumar N, et al. Dentoalveolar distraction osteogenesis for rapid orthodontic canine retraction. J. Int oral Health. 2013 Dec;5(6):31-41.
- [10]. Iyer J, et al. Acquired facial, Maxillofacial and Oral Asymmetries- A review highlighting diagnosis and management. MDPI 15 August. 2021;13(9):1661.

- [11]. David Khechyoyan Y. Orthognathic surgery: General considerations. Semin Plat surg. 2013 Aug;27(3):133 136.
- [12]. Wirthlin JO, Shetye PR. Orthodontists role in orthognathic surgery. SeminPlastSuurg. 2013 Aug;27(3):137-144.
- [13]. Steinbacher DM, et al. Mandibular advancement by distraction osteogenesis for tracheostomy- dependent children with severe micrognathis. J. Oral Maxillofac Surg. 2005 Aug;63(8):1072-1079.
- [14]. Katz EZS, et al. Obstructive sleep Apnea in infants. Am J Respir Crit care Med. 2012 Apr. 15; 185(8): 805-816.
- [15]. Kim Y.K. Complications associated with orthognathic surgery. J Korean Assoc Oral Maxillofac Surg. 2017 Feb;43(1):3-15.
- [16]. Jeong WS, et al. Can a surgery –first orthognathic approach reduce the total treatment time ? Int J Oral Maxillofac. Surg. 2017 Apr; 46(4):473-482.
- [17]. PriyaDevdasNakre, Harikiran AG. Effectiveness of oral heath education programs : Asystematic review. J. Int Soc. Prev Community Dent. 2013 Jul-Dec;3(2):103-115.
- [18]. Kelsey JL, Lamster I.B. Influence of Musculoskeletal conditions on oral health among older adults. AmJ Public Health. 2008 July;98(7):1177-1183.
- [19]. Andrade N. Development and evolution of distraction devices: use of indigenous appliances for distraction osteogenesis – An overview. Annals of Maxillofacial Surgery. 2011 Jan-Jun; 1(1):58-65.
- [20]. Breugem C. Bioresorbable distraction device for the treatment of airway problems for infants with Robin sequence. Clinical oral investigations. 2015 July 10;19:1697.
- [21]. Sesenna E, et al. Mandibular distraction in neonates: indications, technique, results. Ital J Pediatr. 2 Feb 2020;38:7.
- [22]. Maheshwari S, et al. Biomechnics and orthodontic treatment protocol in maxillofacial distraction osteogenesis. Natl J. Maxillofac. Surg. 2011 July Dec;2(2):120-128.
- [23]. Grayson BH, Santiago PE. Treatment planning and biomechanics of Distraction osteogenesis from an orthodontic perspective. Seminars in orthodontics vol. 5, No. 1 (March), 1999, 9-24.
- [24]. Cherian JJ, et al. Mechanical, Anatomical and kinematic axis in TKA : concepts and practical applications. Curr Rev Musculoskelet Med. 2014 Jun;7(2):89-95.
- [25]. Stuik T. Technical feasibility of personalized articulating knee joint distraction for treatment of Tibio femoral osteoarthritis. ClinBiomech (Bristol, Avon). 2017 Nov;49:40-47.
- [26]. Brody-camp S, Winters R. Craniofacial distraction osteogenesis. statpearls publishing. 25 July 2022.
- [27]. Tavakoli K, et al. The role of latency in mandibular osteodistraction. J. Aug;26(4):209-19. Craniomaxillofac surg. 1998
- [28]. Horas K, et al. The role of soft tissue traction forces in bone segment transport for callus distraction strategies. Trauma Limb Reconstr. 2015 Apr;10(1):21-26.

- [29]. Sheen JR, Garla VV. Fracture healing overview. Statpearls Publishing LLC. May 8, 2022.
- [30]. Tandon A, et al. Distraction Osteogenesis in orthodontics. International journal of mechanical engineering. June 2022;7:6.
- [31]. Rachmiel A, Shilo D. The use of distraction osteogenesis in oral and maxillofacial surgery. Annals MaxillofacSurg 2015 Jul-Dec;5(2):146-147.
- [32]. Li Y, et al. Overview of methods for enhancing bone regeneration in distraction osteogenesis: potential roles of biometals. J orthopTranslat. 2021 Mar;27:110-118.
- [33]. Kong LC, et al. An update to the advances in understanding distraction histogenesis : From biological mechanisms to novel clinical applications Journal of Orthopaedic Translation. 25 November 2020, 3-10
- [34]. Wojdasiewicz P, et al. The role of inflammatory and anti inflammatory cytokines in the pathogenesis of osteoarthritis. Mediators Inflamm. 6 Mar 2014, 561459.
- [35]. Kulkari OP, et al. The immune system in tissue environment regaining homeostasis after injury : 1s inflammation always inflammation? Mediators inflamm. Aug 2016, 2856213.
- [36]. Chovatiya R, Medzhitov R. Stress, inflammation and defence of Homeostasis. Mol cell, available in PMC. 2015 Apr 24;54(2):281-288.
- [37]. Lee DY, et al. Mobilisation of endothelial progenitor cells in the healing and distraction osteogenesis. Bone. 2008 May; 42(5):932-941.
- [38]. Marcola M, Rodrigues CE. Endothelial progenitor cells in tumor angiogenesis : Another brick in the wall. Stem cells Int. 2015 Apr. 27:832649.
- [39]. Schipani E, et al. Regulation of osteogenesis Angiogenesis coupling by HIFs and VEGF. J Bone Miner RES. 2009 Aug;24(8):1347-1353.
- [40]. Calvani M, et al. Hypoxic induction of an HIF- 1 alpha- dependent Bfgf autocrine loop drives angiogenesis in human endothelial cells. Blood.2006 Apr.1;107(7):2705 2712.
- [41]. Akaogi Jun. Prostaglandin E2 receptors EP2 and EP4 are upregulated in peritoneal macrophages and joints of pristine- treated mice and modulate TNF- alpha and IL-6 production. J. Leukoc Biol. 2004 Jul;76(1):227-36.
- [42]. Stamnitz S, Klimczak A. Mesenchymal stem cells, bioactive factors and scaffolds in bone repair: MDPI. 2021 Aug;10(8):1925.
- [43]. Hego AF, Shuman MA. Distraction osteogenesis of the maxillofacial skeleton: Biomechanics and clinical implications. Open Access Scientific Reports. 2012;1(11):509.
- [44]. Rajiv Agarwal. Unfavourable results with distraction in craniofacial skeleton. Indian J Plast surg.2013 May Aug;46(2):194-203.
- [45]. Mohanty R, et al. Vertical alveolar ridge augmentation by distraction osteogenesios. J ClinDiagn Res. 2015 Dec 1;9(12):ZC 43-ZC46.
- [46]. Shyam AK, et al. Leg lengthening by distraction osteogenesis using the Ilizarov apparatus: a novel concept of tibia casllus subsidence and its influencing factors. IntOrthop. 2009 Dec;33(6):1753-1759.

- [47]. Kusec V, et al. Distraction osteogenesis by Ilizarov and unilateral external fixators in a canine model. International orthopaedics (SICOT). 2003;27:47-52.
- [48]. AnirejuoritseBafor. Distraction osteogenesis: A review of the literature. Nigerian journal of orthopaedics and trauma. January-june 2020;19(1):1.
- [49]. Rachmiel A, et al. Management of obstructive sleep apnea in pediatric craniofacial anomalies. Annals of Maxillofacial surgery. July-December 2012;2(2):111 115
- [50]. Jiang N, et al. Periodontal ligament and alveolar bone in health and adaptation: Tooth movement: Front oral Biol. 2016;18:1-8.
- [51]. Sanivarapu S, et al. Periodontally accelerated osteogenic orthodontics: Novel perio-ortho interrelationship. J Indian socPeriodontol. 2018 Sep-Oct; 22(5):459-462.
- [52]. Yang L, et al. Alveolar distraction osteogenesis. A systemic literature review. Mahidol Dental journal. 2014;34(03):289-300.
- [53]. Vedavathi HK, et al. The role of orthodontist in distraction osteogenesis. Indian journal of orthodontics and dentofacial research, july-sept. 2017;3(3):141-147.
- [54]. Ulrike BU, et al. Mandibular midline distraction osteogenesis. Oral health dent Manag. 2013;12(4):532.
- [55]. Da. Silveira A, et al. Orthodontic considerations for maxillary distraction osteogenesis in growing patients with cleft lip and palate using internal distractors. SeminPlast Surg. 2014 Nov;28(4):207-212.
- [56]. Chu TMG, et al. Segmental bone regeneration using a load bearing biodegradable carrier of bone morphogenetic protein-2; Jan 2007;28(3):459-467.
- [57]. Fu R, et al. Mechanical regulation of bone regeneration during distraction osteogenesis. Medicine in novel technology and devices; 27 April 2021.
- [58]. Alvarez K, Nakajma H. Metallic scaffolds for bone regeneration. Biocompatibitity of materials. 2009;2(3):790-832.
- [59]. Grayson BH, et al. Treatment planning and biomechanics of distraction osteogenesis from an orthodontic perspective. Seminorthod. 1999 Mar;5(1):9-24.
- [60]. Hu XX, et al. Effectiveness of transverse tibial bone transport in treatment of diabetic foot ulcer : A systematic review and meta-analysis. Front Endocrinol (Lausanne). 2022;13:1095361.
- [61]. Nie X. Tibial cortex transverse transport facilitating healing in patients with recalcitrant non-diabetic leg ulcers. J OrthopTranslat. 2021 Mar;27:1-7.
- [62]. Kong LC. An update to the advances in understanding distraction histogenesis: From biological mechanisms to novel clinical applications. Journal of orthopaedic translation. Nov 2020;25:3-10.
- [63]. Guang Yang, et al. Tendon and ligament regeneration and repair: clinical relevance and development paradigm. Birth defects Res C. Embryo Today. 2013 sep;99(3):203 222.