

Original Article

Contents lists available at [ScienceDirect](www.sciencedirect.com/science/journal/10139052)

The Saudi Dental Journal

journal homepage: www.ksu.edu.sa www.sciencedirect.com

Evaluation of flat ridge rehabilitation using an intraoral custom-made distraction device at four weeks versus eight weeks and its impact on dental implant efficacy: A comparative study

Sherif S. Hassan ^{a,b}, Mohamed A. Shuman ^c, Alaa Z. Makke ^d, Alaa W. AlQutub ^{e,*}, Ibraheem K. Bamaga ^a, Reda A. Nofal ^{c,e}, Mohammed H. Al-Kabany ^{e,f}

a Department of Basic and Clinical Oral Sciences, Faculty of Dental Medicine, Umm Al-Qura University, Makkah, Saudi Arabia

^b *Department of Oral Biology and Dental Anatomy, Faculty of Dentistry, Al-Azhar University, Egypt*

^c *Department of Oral & Maxillofacial Surgery, Faculty of Dentistry, Al-Azhar University, Egypt*

^d Department of Oral and Maxillofacial Surgery (Dental Implantology), Faculty of Dental Medicine, Umm Al-Qura University, Makkah, Saudi Arabia

^e Department of Oral and Maxillofacial Surgery, Faculty of Dental Medicine, Umm Al-Qura University, Makkah, Saudi Arabia

^f *Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Cairo University, Egypt*

ARTICLE INFO

Keywords: Distraction **Osteogenesis** Dental implant Consolidation Osseointegration

ABSTRACT

Background: This study aimed to evaluate alveolar bone height enhancement using a custom-made distractor to evaluate its ability to support dental implants.

Method: The left mandibular premolars of nine dogs were extracted, followed by alveoloplasty to simulate an atrophic ridge. The dogs were divided into three groups: groups I and II received distractors followed by dental implants, while group III received implants alone. Distractors remained in place for 4 weeks in group I and 8 weeks in group II for consolidation. Subsequently, the distractors were removed, and a titanium dental implant was immediately inserted during the same visit. In the third group, implants were placed in the same area as noted. The implant was left in position for 8 weeks, after which the left hemimandible underwent dual-energy Xray absorptiometry and histological analysis, focusing on the region of interest $(ROI)^{\perp}$ mesial and distal to the dental implant.

Results: Densitometric analysis revealed notable osseointegration between the regenerated bone adjacent to the dental implant. Notably, there were significant differences in osseointegration between groups I and II. Moreover, osseointegration levels were similar between groups II and III, where no distraction device was employed. Histological findings showed the formation of new bone in the distraction gap, with more advanced maturation noted in the 8-week group. It is worth noting that the integration between bone and implants in the third group surpasses that of the distraction groups.

Conclusion: Using the distraction device for only 4 weeks is acceptable to meet the criteria for implant placement. The small size of the distraction device reduces tissue reaction after surgery because it eliminates the necessity of complex surgeries that may require bone grafting. Density measurements and histological observations indicate that the distractor promotes the generation of enough bone for prosthetic rehabilitation with dental implants.

E-mail address: awqutub@uqu.edu.sa (A.W. AlQutub).

<https://doi.org/10.1016/j.sdentj.2024.07.007>

Received 7 March 2024; Received in revised form 2 July 2024; Accepted 4 July 2024

Available online 6 July 2024

1013-9052/© 2024 THE AUTHORS. Published by Elsevier B.V. on behalf of King Saud University. This is an open access article under the CC BY-NC-ND license [\(http://creativecommons.org/licenses/by-nc-nd/4.0/\)](http://creativecommons.org/licenses/by-nc-nd/4.0/).

^{*} Corresponding author at: Department of Oral and Maxillofacial Surgery, Faculty of Dental Medicine, Umm Al-Qura University, P.O. Box 715, Makkah 24238, Saudi Arabia.

Abbreviations:

ROI., Region of interest; DO., Distraction osteogenesis; DEXA., Dual-energy x-ray absorptiometry; BMC., Bone mineral content; BMD., Bone mineral density; ANOVA., Analysis of variance.

1. Introduction

Replacing teeth in flat alveolar ridges poses challenges in determining appropriate dental implant to meet both functional and aesthetic requirements (Bras et al., 1983). For effective mandibular rehabilitation, the height of the edentulous ridge above the mandibular canal must be at least 7 mm [\(Keller,](#page-5-0) 1995). Common etiological factors for a flat alveolar ridge include tooth loss, periodontal disease, tumor removal, and post-traumatic growth disorders ([Chang](#page-5-0) et al., 2016). Distraction osteogenesis is a surgical approach that involves osteotomy to generate a gap by utilizing the bone's regenerative capacity to elongate the alveolar ridge (Toledano et al., 2019; Vale et al., [2020](#page-6-0)). The distraction device is distinguished from other grafting techniques in that it enhances the size of the original bone (Ilizarov, 1988; [Kobayashi](#page-5-0) et al., 2005; Nelson et al., 2006; [Zapata](#page-5-0) et al., 2014). [Codivilla](#page-5-0) was the first to use a distractor device on bones in 1905 (Hosny, 2020), while [McCarthy](#page-5-0) et al. (1992) was the first used this device for lengthening maxillofacial bones. The mechanism of DO originate from traction, inducing tension within the callus and prompting the formation of a new bone aligned with the distraction vector (Lim et al., 2018; [Pereira](#page-5-0) et al., 2007). The primary advantage of the distraction device over traditional surgical approaches is its ability to reduce wound dehiscence by maintaining periosteal nutrition of the bony rim ([Chiapasco](#page-5-0) et al., 2006; Gaggl et al., 2000).

The process of bone formation via distraction involves several biological phases: latency, distraction, and consolidation (Cho et al., [2007;](#page-5-0) [Pereira](#page-5-0) et al., 2007). In the latency phase, the clot transforms into granulation tissue, containing connective tissue cells and infiltrating capillaries, progressing to form smooth calluses within a few days. Interleukin (IL-1) secreted by progenitor cells plays a critical role in the inflammatory response while interleukin (IL-6) stimulates mesenchymal stem cell proliferation (Ando et al., [2014;](#page-5-0) Yang et al., 2022). Numerous studies have reported increased expression of TGF-β1 during both the latency and distraction phases, reaching levels more than twice as high as those found in the normal mandible ([Alzahrani](#page-5-0) et al., 2014; Weiss et al., [2002;](#page-5-0) Yang et al., 2022). Many studies have indicated that an appropriate latency period of 5–7 days significantly influences optimal healing [\(Jensen](#page-5-0) et al., 2002; Mofid et al., 2001).

The distraction phase involves exerting tensile forces on the gap tissue, with the proliferation of fibroblast-like cells at the peripheries ([Jazrawi](#page-5-0) et al., 1998). At the distraction gap, TGF-β1 secreted by stem cells stimulates osteoblast proliferation to fill the gap ([Ozkan](#page-5-0) et al., [2007\)](#page-5-0). During the distraction phase, the expression of many bone morphogenic proteins (BMP-2,4,7) is upregulated, followed by a sub-sequent decrease during consolidation stage [\(Cheung](#page-5-0) et al., 2006; [Marukawa](#page-5-0) et al., 2006). Numerous studies suggest that a rate of 1 mm daily leads to sufficient bone formation in maxillofacial distraction osteotomies (Fu et al., 2021; Klein and [Howaldt,](#page-5-0) 1996). In 1989, Ilizarov reported that a movement rate of 0.5 mm/day results in early consoli-dation, ultimately leading to the failure of the distraction plan ([Ilizarov,](#page-5-0) [1989\)](#page-5-0). Conversely, increasing the rate of movement to 2 mm/day may result in compromised bone formation and inadequate adjustment of soft tissues (Natu et al., 20214). After cessation of the distraction phase, the regenerated bone undergoes maturation that typically lasts 3–4 weeks in children and 6–8 weeks in adults (Yen et al., [2020](#page-6-0)). [Karp](#page-5-0) et al. [\(1992\)](#page-5-0) examined mandibular elongation over consecutive days and noted the presence of three distinct layers spanning from the center to the peripheries of the gap. The central area of the gap consists of fibrous tissue with fibroblast-like cells; the subsequent layer denotes the site of bone formation surrounded by osteoblast cells; and the third layer, the layer of remodeling, ultimately leads to the creation of mature bone (Karp et al., [1992](#page-5-0)). Dual-energy x-ray absorptiometry (DEXA) is a critical method for assessing both BMC and BMD, which helps in making informed therapeutic decisions and evaluating treatment responses ([Lorente-Ramos](#page-5-0) et al., 2012). The current study aims to evaluate the histological structure and densitometric analysis of newly formed bones using a custom-made distraction device for a brief period and its ability

to receive dental implants to reduce the time required for prosthodontics.

2. Materials and methods

2.1. Grouping and scenario

University, Cairo, Egypt. The experiment began with the extraction of premolars, followed by alveoloplasty to flatten the ridge. The dogs were divided into three groups: Groups I and II underwent osteotomy and installation of distraction devices. After seven days, the distractor was rotated two full revolutions daily until a vertical height of 7 mm was achieved. Subsequently, the consolidation period was extended to 4 weeks for Group I and 8 weeks for Group II. Afterward, the third surgery was performed to remove the distractor and insert the dental implants. The dogs in Group III received only dental implants of the appropriate size. The osseointegration process began with dental implants and lasted 8 weeks for all groups.

2.2. Extraction and alveoloplasty

For the first surgery, the animals were anesthetized using sodium thiopental at 40 mg/kg (Pharm. Industry Co. Egypt) into the recurrent tarsal vein. The procedure involved extracting the lower left premolars, reducing the height of the alveolar bone, trimming the excess mucosa, and suturing it with a 4/0 chromic catgut suture. After consuming soft food for one week, the dogs were made to resume their regular diet and left for 12 weeks for complete healing.

2.3. Osteotomy and distraction

The second surgery was performed to insert a titanium distraction device that consisted of two small plates interconnected by a threaded rod (Fig. 1). The lower plate of the distractor was secured to the base of the mandibular body, the transport plate was fixed to the induced movable bone segment.

Fig. 1. Installation of the distractor device with eight screws (a), cutting line (b), and inserting the dental implant (c).

Dogs in Groups I and II were anesthetized, and a semicrestal buccal flap was created. Careful subperiosteal dissection was performed to preserve the lingual mucosa. The distractor was customized according to the mandibular topography. A bone segment measuring 30 mm in length and 5 mm in height was designated for distraction, with holes drilled at appropriate positions for screw placement, followed by separation from the jaw. Both distractor pieces were fastened in place using eight titanium screws, the surgery area was sutured with 4/0 chromic catgut suture ([Fig.](#page-1-0) 1). The animals were administered Zyleject (Amoun Pharm. Co., Cairo, Egypt) twice daily for 3 days, with Amoxicillin 500 mg (Egyptian Pharmaceutical Co., 10th of Ramadan, Egypt) twice daily for 5 days. After 1 week, the distraction spring was rotated clockwise for two full revolutions daily for seven days until it was extended coronally by 7 mm, and the designated consolidation period began.

2.4. Distraction removal and implant insertion

In the third surgical procedure, the distractor was extracted from Groups I and II, and a dental implant of 15×4.9 mm (Tot II Dent, Alexandria, Egypt) was placed at the focal point. A dental implant of 11 \times 4.9 mm was performed on Group III at a suitable site [\(Fig.](#page-1-0) 1). After 8 weeks, all dogs were euthanized by cardiac injection of pentobarbital. The entire lower jaw was removed and divided equally into two parts.

2.5. DEXA analysis

Hemimandibles containing implants were utilized to calculate BMC and BMD using a DEXA device (Norland Eclipse Norland® densitometer, USA). The ROI encompasses three points mesial and distal to the implant. The distal point was located 8 mm from the upper mandibular rim, whereas the mesial points were positioned 2 mm coronally and apically to the distal point. After selecting the targeted area with a pointer, the program recorded the volume (in $\rm cm^3$), BMC (in g), and BMD (in g/cm^3).

2.6. Histologic evaluation

The specimens were fixed in a 10 % neutral formalin for 10 days, then immersed in a mixture of 20 % sodium citrate and 5 % formic acid for 2 months for decalcification. Each decalcified sample was embedded in molten paraffin and allowed to solidify, after which the implant was carefully extracted. Serial sections were cut and stained with H&E and trichrome stain to analyze the newly formed bone.

Data analysis was performed using SPSS version 23 (IBM, USA). The ANOVA test was obtained to determine the significant relationship (*P <* 0.05). Tukey's HSD test was performed to determine significant relations among the groups.

3. Results

All surgeries went smoothly, and recovery was uneventful without complications. All implants were successfully positioned without rejection. Throughout the healing and osseointegration process, the mucous membrane remained free from inflammation.

3.1. Densitometric analysis

The goal of measuring BMC and BMD was focused on the area mesial and distal to the dental implant, represented by the stars (*) (Fig. 2). Statistical analysis was performed on the recorded data from all groups utilizing Kolmogorov–Smirnov and Shapiro–Wilk tests and the normality of the data distribution was also evaluated (Chart 1). The results of the ANOVA test for BMC and BMD showed statistically significant differences between all groups, $p = 0.000$ and $P = 0.014$, respectively [\(Table](#page-3-0) 1). Multiple comparisons through the Tukey HSD test indicated significant differences among all groups of both BMC and BMD, except BMD, between Groups II and III (*p* = 0.164) [\(Table](#page-3-0) 2).

3.2. Histological examination

Histological examination of the ROI of group I revealed diverse stages of bone formation in distinct regions. The initial layer comprises mature lamellar bone oriented toward the base of the mandible, characterized by numerous osteocytes arranged in a definitive pattern and

Chart 1. Means of BMC and BMD of all groups.

Fig. 2. Print out scanner photographs of densitometric analysis of implants of all groups, * represent the ROI.

Table 1

One way of variance (ANOVA) test of both BMC and BMD.

BMC $\overline{2}$.003 .001 325.406 Between Groups	.000
Within Groups .000 6 .000	
Total 8 .003	
$\mathbf{2}$.029 126.165 .014 BMD Between Groups	.000
Within Groups 6 .001 .000	
Total 8 .030	

multiple reversal lines facing the mandibular bone. This is followed by a layer of bone undergoing maturation, which is succeeded by a final layer of immature woven bone contacting the implant threads with osteocyte cells. Examination with Masson's trichrome staining revealed that the

Table 2

Multiple comparison Tukey HSD and Dunnett t (2-sided) between groups.

bone adjacent to the mandible exhibited a mature type, as indicated by the green staining. In contrast, the area of the woven bone facing the implant displayed red staining of immature ossification (Fig. 3).

Histological sections of group II revealed the emergence of a fine sheet of woven bone directed toward the implant screws. This was succeeded by a broad, clearly delineated layer of mature lamellar bone with multiple bone marrow spaces. These spaces were demarcated from the mandibular base by reversal lines, indicative of ongoing bone remodeling activity. Masson's trichrome staining highlighted the presence of mature calcified bone, which was represented by green staining near the base of the jaw, followed by a mixture of green and red colors within the bone tissue, indicating the continuous process of bone maturation [\(Fig.](#page-4-0) 4).

Histological sections of Group III revealed an area of small cylindrical lamellar bone facing the implant threads containing osteocytes demarcated from the next layer by the reverse line. The second layer was a layer of mature cancellous bone with bony trabeculae and areas of bone marrow; it homogeneously continued with the spongiosa of the

*. The mean difference is significant at the 0.05 level.

a. Dunnett t-tests treat one group as a control and compare all other groups against it.

Fig. 3. Photomicrographs of Group I show basal bone with definite osteocyte cells (A), line of separation between old and mature bone (B), area of indefinite bone remodeling (C), scattered mature osseointegration of green staining (D), red staining of fibrous tissue. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Fig. 4. Photomicrographs of Group II show spongy bone with marrow spaces (A), mature lamellar bone-facing implant threads (B), definite osteocyte cells (C), osseointegration of green staining (D), a mix of green & red staining, (E) at area facing the implant (F). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

body of the mandible. Trichrome staining revealed the appearance of fully matured calcified bone in the form of green staining all over the thickness (Fig. 5).

4. Discussion

DO is a tissue engineering technique that employs tension mechanics to prompt the formation of bone tissue within the created gap. The latest research underscores the reliability of DO as a surgical approach to enhance the height of alveolar ridges during 4-week and 8-week consolidation periods. It demonstrates its ability to create an optimal environment for placing dental implants within a short duration. Conventional distractors typically align screw holes in a parallel manner in both the movable and fixed parts. However, in the current design, each part of the distraction device is fixed with four screws. In the part fixed to the base of the jaw, the orientation of the screw holes is perpendicular to that of the movable part. In addition, instead of a single line, the four

screw holes are arranged in two parallel lines, with two holes in each. This modification is intended to enhance the geometric stability of the distractor, thus reducing the possibility of inappropriate buccal–lingual rotation.

In this study, a bone section 30 mm in length and 5 mm in height was cut to be sufficient to achieve distractor stability with a successful blood supply. A thin titanium distractor was made and fixed in the appropriate position to ensure the integrity of the buccal mucoperiosteum. This integration is critical to maintaining the mesenchymal stem cells needed for bone regeneration in the biological environment to ensure optimal outcomes. The distraction arm was rotated two full revolutions clockwise to lengthen 1 mm daily for 7 days to lengthen 7 mm. The biological results were consistent with this daily tensile strength. Relevant results for most investigators indicated that adequate amounts of calcified lamellar bone were achieved using daily stimulation with a single movement of 1 mm (Bell et al., 1997; [Chiapasco](#page-5-0) et al., 2006; Gaggl et al., 2000; [Ilizarov,](#page-5-0) 1989; Meyer et al., 2001). Although other researchers

Fig. 5. Photomicrographs of Group III show spongy bone with bone marrow spaces (A), mature lamellar bone-facing implant threads with definite osteocyte cells (B), and reversal lines between spongy, compact bone indicating bone remodeling (C), mature osseointegration of green staining (D), and pink staining of Haversian's canal (E). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

have agreed that the target movement rate was 1 mm/day, it should be divided into 0.5 mm twice /day (Block et al., 1996; Green et al., 2005). Furthermore, several authors performed one revolution of 1 mm daily for over 10 days to attain 10 mm. They observed mechanical instability, resulting in microvascular disruption (Bras et al., 1988; Green et al., 2005). In contrast, Ilizarov (1989) reported that a decrease in the movement rate to 0.5 mm/day leads to early consolidation and, thus, failure of the targeted distraction plan (Ilizarov, 1989).

An ongoing controversy continues regarding the minimum duration necessary for the consolidation period, which is sufficient for generating mature bone tissue capable of supporting dental implants. According to current research, a consolidation period of 4 weeks is suitable, as bone maturation progresses, facilitating the placement of a fixed dental implant within a noninflammatory environment, supported by healthy overlying mucosa. This period is similar to the one recorded by [Ransom](#page-6-0) et al. [\(2018\),](#page-6-0) who determined that 43 days ($5 + 10 + 28$ days) from the start of distractor installation until its removal [\(Ransom](#page-6-0) et al., 2018). Other experiments have shown a wide range of the time required to close the gap, reaching 12 weeks, which appears to depend on the animal used and the bone tissue (Li et al., 1999; Richards et al., 2000). Histological and histochemical examination indicated that the newly formed bone in the distraction gap had a wide extent of maturation needed for osseointegration in the 4-week and 8-week groups, with the latter displaying a higher degree of maturation, suggesting that the periods employed for DO in each group were sufficient to prepare the site for accommodating a dental implant.

5. Conclusion

DO is a successful surgery that leads to the formation of bone tissue within the flat ridge in a short period, making it suitable for accommodating dental implants without the need for bone grafting. Densitometry measurements and histological observations demonstrated that bone formation in both distracted groups resulted in sufficient bone tissue formation, enabling the successful rehabilitation of dental implant prosthetics with a satisfactory success rate.

6. Financial support

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethics approval

The Ethics Committee of the Faculty of Dentistry, Al-Azhar University, Egypt, agreed to conduct the research under the number (ALAREC20230001-1).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

Additional data are available on request from the corresponding author.

References

- Ando, Y., et al., 2014. Stem cell-conditioned medium accelerates distraction osteogenesis through multiple regenerative mechanisms. Bone 61, 82–90. [https://doi.org/](https://doi.org/10.1016/j.bone.2013.12.029) [10.1016/j.bone.2013.12.029](https://doi.org/10.1016/j.bone.2013.12.029) [PubMed].
- Bell, W., et al., 1997. Distraction osteogenesis to widen the mandible. Br. J. Oral Maxillofacial Surg. 35 (1), 11–19. [https://doi.org/10.1016/s0266-4356\(97\)90003-6](https://doi.org/10.1016/s0266-4356(97)90003-6) [PubMed].
- Block, M., et al., 1996. Bifocal distraction osteogenesis for mandibular defect healing. J. Oral Maxillofacial Surgery 54 (11), 1365–1370. [https://doi.org/10.1016/](https://doi.org/10.1016/s02782391(96)-90499-1) [s02782391\(96\)-90499-1](https://doi.org/10.1016/s02782391(96)-90499-1) [PubMed].
- Bras J., et al., 1988. Mandibular atrophy and metabolic bone loss. A radiologic analysis of 126 edentulous patients. Int. J. Oral Surg. 12(5), 309-13. doi: [10.101](https://doi.org/10.1016/s0300-9785(83)80018-0) [6/s0300-9785\(83\)80018-0](https://doi.org/10.1016/s0300-9785(83)80018-0) [PubMed].
- Chang, H., et al., 2016. Alveolar distraction osteogenesis. J. Dent. Sci. 11 (2), 212–213. <https://doi.org/10.1016/j.jds.2016.02.003> [PubMed].
- Cheung, L., et al., 2006. Effect of distraction rates on the expression of bone morphogenetic proteins in rabbit mandibular distraction osteogenesis. J. Cranio-Maxillo-Facial Surgery 34 (5), 263–269. [https://doi.org/10.1016/j.](https://doi.org/10.1016/j.jcms.2006.02.004 [PubMed]) [jcms.2006.02.004](https://doi.org/10.1016/j.jcms.2006.02.004 [PubMed]) [PubMed].
- Chiapasco, M., et al., 2006. Quality and quantity of bone following alveolar distraction osteogenesis in the mandible. Clin. Oral Implants Res. 17 (4), 394–402. [https://doi.](https://doi.org/10.1111/j.1600-0501.2005.01247.x) [org/10.1111/j.1600-0501.2005.01247.x](https://doi.org/10.1111/j.1600-0501.2005.01247.x) [PubMed].
- Cho, T., et al., 2007. Expression and role of interleukin-6 in distraction osteogenesis. Calcified Tissue Int. 80 (3), 192–200. <https://doi.org/10.1007/s00223-006-0240-y> [PubMed].
- Codivilla, A., 2008. The classic: on the means of lengthening, in the lower limbs, the muscles and tissues which are shortened through deformity. Clin. Orthopaedics Related Res. 466 (12), 2903–2909. <https://doi.org/10.1007/s11999-008-0518-7> [PubMed].
- Gaggl, A., et al., 2000. Vertical alveolar ridge distraction with prosthetic treatable distractors: a clinical investigation. Int. J. Oral Maxillofac Implants 15(5), 701-10. [PubMed].
- Green, E., et al., 2005. Risk factors, treatment, and outcomes associated with nonunion of the midshaft humerus fracture. J. Surg. Orthop. Adv. 14(2), 64-72. [PubMed].
- Ilizarov, G.A., 1988. The principles of the Ilizarov method. Bull. Hosp. Jt. Dis. Orthop. Inst. 48(1), 1-11. [PubMed].
- Ilizarov, G.A., 1989. The tension-stress effect on the genesis and growth of tissues. Part I. The influence of stability of fixation and soft-tissue preservation. Clin. Orthop. Relat. Res. 238, 249-81. [PubMed].
- Jazrawi, L., et al., 1998. Bone and cartilage formation in an experimental model of distraction osteogenesis. J. Orthopaedic Trauma 12 (2), 111–116. [https://doi.org/](https://doi.org/10.1097/00005131-199802000-00008) [10.1097/00005131-199802000-00008](https://doi.org/10.1097/00005131-199802000-00008).
- Jensen, O., et al., 2002. Anterior maxillary alveolar distraction osteogenesis: a prospective 5-year clinical study. Int. J. Oral Maxillofac. Implants 17(1), 52-68. [PubMed].
- Karp, N.S., et al., 1992. Membranous bone lengthening: a serial histological study. Ann. Plastic Surgery 29 (1), 2–7. <https://doi.org/10.1097/00000637-199207000-00002> [PubMed].
- Keller, E.E., 1995. Reconstruction of the severely atrophic edentulous mandible with endosseous implants: a 10-year longitudinal study. J. Oral Maxillofacial Surg. 53 (3), 305–320. [https://doi.org/10.1016/0278-2391\(95\)90231-7](https://doi.org/10.1016/0278-2391(95)90231-7) [PubMed].
- Klein, C., Howaldt, H.P., 1996. Correction of mandibular hypoplasia by means of bidirectional callus distraction. J. Craniofacial Surg. 7 (4), 258–266. [https://doi.org/](https://doi.org/10.1097/00001665-199607000-00002) [10.1097/00001665-199607000-00002](https://doi.org/10.1097/00001665-199607000-00002) [PubMed].
- Kobayashi, E., et al., 2005. Effects of the placement of endosseous implants in vascularized bone grafts on bone in dogs. Int. J. Oral Maxillofacial Surgery 34 (6), 659–667. [https://doi.org/10.1016/j.ijom.2005.02.001.](https://doi.org/10.1016/j.ijom.2005.02.001)
- Li, G., Simpson, A., et al., 1999. Effect of lengthening rate on angiogenesis during distraction osteogenesis. J. Orthopaedic Res. 17 (3), 362–367. [https://doi.org/](https://doi.org/10.1002/jor.1100170310) [10.1002/jor.1100170310](https://doi.org/10.1002/jor.1100170310) [PubMed].
- Lim, H., et al., 2018. Application of autologous human bone marrow-derived mesenchymal stem cells in distraction osteogenesis for the treatment of bilateral mandibular hypoplasia. J. Craniofacial Surgery 29 (6), 1629–1632. [https://doi.org/](https://doi.org/10.1097/SCS. 00000000-00004614) 10.1097/SCS. [00000000-00004614](https://doi.org/10.1097/SCS. 00000000-00004614).
- Lorente-Ramos, R., et al., 2012. Dual-energy X-ray absorptiometry: fundamentals, methodology, and clinical applications. Radiología 54 (5), 410–423. [https://doi.org/](https://doi.org/10.1016/j.rx.-2011.09.023) [10.1016/j.rx.-2011.09.023](https://doi.org/10.1016/j.rx.-2011.09.023) [PubMed].
- Marukawa, K., et al., 2006. Expression of bone morphogenetic protein-2 and proliferating cell nuclear antigen during distraction osteogenesis in the mandible in rabbits. Br. J. Oral Maxillofacial Surg. 44 (2), 141–145. [https://doi.org/10.1016/j.](https://doi.org/10.1016/j.bjoms.2005.-04.009) [bjoms.2005.-04.009](https://doi.org/10.1016/j.bjoms.2005.-04.009) [PubMed].
- McCarthy, J., et al., 1992. Lengthening the human mandible by gradual distraction. Plast Recons. Surg. 89(1), 1-8. [PubMed].
- Meyer, U., et al., 2001. Mechanical tension in distraction osteogenesis regulates chondrocytic differentiation. Int. J. Oral Maxillofacial Surgery 30 (6), 522–530. <https://doi.org/10.1054/ijom.2001.0159> [PubMed].
- Mofid, M., et al., 2001. Craniofacial distraction osteogenesis: a review of 3278 cases. Plastic Reconstructive Surgery 108 (5), 1103–1114. [https://doi.org/10.1097/-](https://doi.org/10.1097/-00006534-200110000-00001) [00006534-200110000-00001](https://doi.org/10.1097/-00006534-200110000-00001) [PubMed].
- Nelson, K., et al., 2006. Clinical evaluation of endosseous implants in nonvascularized fibula bone grafts for reconstruction of severely atrophied mandibular bone. J. Oral Maxillofacial Surgery 64 (9), 1427–1432. [https://doi.org/10.1016/j.](https://doi.org/10.1016/j.joms.2006.05.035) [joms.2006.05.035](https://doi.org/10.1016/j.joms.2006.05.035) [PubMed].
- Ozkan, K., et al., 2007. Effect of transforming growth factor beta1 (TGF-beta1) on regenerate bone in distraction osteogenesis. Growth Factors 25 (2), 101–107. <https://doi.org/10.1080/08977190701352594> [PubMed].

Alzahrani, M., et al., 2014. The effect of altering the mechanical loading environment on the expression of bone regenerating molecules in cases of distraction osteogenesis. Front. Endocrinol. (Lausanne) 5, 214. <https://doi.org/10.3389/fendo.2014.00214> [PubMed].

- Pereira, M., et al., 2007. Understanding distraction osteogenesis on maxillofacial complex: a literature review. J. Oral Maxillofacial Surgery 65 (12), 2518–2553. [https://doi.org/10.1016/j.joms.2006.10.019.](https://doi.org/10.1016/j.joms.2006.10.019)
- Ransom, R., et al., 2018. Mechanoresponsive stem cells acquire neural crest fate in jaw regeneration. Nature 563 (7732), 514–521. [https://doi.org/10.1038/s41586-018-](https://doi.org/10.1038/s41586-018-0650-9) [0650-9](https://doi.org/10.1038/s41586-018-0650-9) [PubMed].
- Richards, M., et al., 2000. Increased distraction rates influence precursor tissue composition without affecting bone regeneration. J. Bone Mineral Res. 15 (5), 982–989. <https://doi.org/10.1359/jbmr.2000.15.5.982> [PubMed].
- Vale, F., et al., 2020. Distraction osteogenesis in a dog with a tooth-borne device: Histological and histomorphometric analysis. J. Clin. Exp. Dentistry 12 (1), e52–e58. <https://doi.org/10.4317/medoral.56491> [PubMed].
- Weiss, S., et al., 2002. Systemic regulation of distraction osteogenesis: a cascade of biochemical factors. J. Bone Mineral Res. 17 (7), 1280–1289. [https://doi.org/](https://doi.org/10.1359/jbmr.2002.17.7.1280) [10.1359/jbmr.2002.17.7.1280](https://doi.org/10.1359/jbmr.2002.17.7.1280) [PubMed].
- Yang, S., et al., 2022. Immunomodulatory effects, and mechanisms of distraction osteogenesis. Inte. J. Oral Sci. 14 (1), 4. [https://doi.org/10.1038/s41368-021-](https://doi.org/10.1038/s41368-021-00156-y) [00156-y](https://doi.org/10.1038/s41368-021-00156-y) [PubMed].
- Yen, S., et al., 2020. Orthodontic and surgical principles for distraction osteogenesis in children with Pierre-Robin sequence. Oral Maxillofacial Surg. Clin. North America 32 (2), 283–295. <https://doi.org/10.1016/j.coms.2020.01.012> [PubMed].
- Zapata, U., et al., 2014. Biomechanics of the canine mandible during bone transport distraction osteogenesis. J. Biomech. Eng. 136 (11) [https://doi.org/10.1115/](https://doi.org/10.1115/1.4028409) [1.4028409](https://doi.org/10.1115/1.4028409) [PubMed].