Journal of the Pediatric Orthopaedic Society of North America 7 (2024) 100056

Contents lists available at ScienceDirect

Journal of the Pediatric Orthopaedic Society of North America

journal homepage: www.jposna.com

Pediatric Bone Health Update

Importance of bone health in bone lengthening

Christopher Iobst, MD, FAAOS, FAOA[1,*], Anirejuoritse Bafor, MBBS, FMCS, FMCOrtho, FACS[1], John E. Herzenberg, MD, FRCSC, FAAOS[2]

[1] Nationwide Children's Hospital, Columbus, OH, USA
[2] Rubin Institute for Advanced Orthopedics, Sinai Hospital of Baltimore, Baltimore, MD, USA

ARTICLE INFO

Keywords:
Distraction
Osteogenesis
Regenerate
Bone
Quality

ABSTRACT

Distraction osteogenesis describes the process of growing new bone ("regenerate") to correct limb length discrepancies or limb deformities. Whether pure lengthening or a combination of lengthening and straightening is involved, this represents one of the highest anabolic demands on bone in orthopedic surgery. Because distraction osteogenesis requires the formation of new bone, often in large amounts, it is critically important to evaluate the bone health of any potential surgical patient. Patients undergoing limb lengthening, therefore, would be expected to be especially sensitive to poor bone health. This article will review opportunities to assess and potentially improve bone health for limb lengthening patients.

Key Concepts:

(1) Many potential limb lengthening patients may be vitamin D deficient or insufficient.
(2) Other simple nutraceuticals such as Boron, Magnesium, Calcium, Silicon, vitamin K, L-arginine, and Inositol should be considered as adjuncts to bone health.
(3) Intra-operative technique such as minimally invasive incisions that protect the blood supply and periosteum combined with osteotomies that maximize the bone surface area are recommended.
(4) Numerous proposed pharmacological and mechanical interventions to improve and accelerate the healing of the regenerate bone look promising but are still investigational.

Introduction

Bone is a metabolically active tissue that undergoes continuous cycles of remodeling during an individual's lifetime. Besides providing structure and support, our bones are an important reservoir for calcium, phosphate, and essential ions for homeostatic mechanisms. The formation of healthy normal bone during the process of distraction osteogenesis is dependent on an intricate balance between multiple factors including the health of other organs and systems, such as the liver, the kidneys, the gastrointestinal tract, and the immune system [1,2]. Therefore, it is not surprising that there is an increased risk of complications such as surgical site infection in malnourished patients undergoing major orthopedic surgery [3]. Consequently, a thorough preoperative assessment and optimization of bone health and nutrition is essential for best outcomes in distraction osteogenesis.

Pre-operative assessment of the limb reconstruction patient

Distraction osteogenesis places a substantial anabolic load on the body. Therefore, an evaluation of the patient's general nutritional status and the optimization of vitamin D levels, albumin levels, white blood cell count, and transferrin may be an important initial consideration in the management of patients undergoing limb lengthening and reconstruction surgery. The subtle presentation of some nutritional deficiencies, particularly in the initial stages of the disease, argues for a preoperative assessment of the nutritional status of patients planned for limb lengthening. It has been shown that major orthopedic surgery results in a decrease in nutritional markers in as little as 24–48 hours following surgery which adds to the value of the pre-operative assessment [4]. When limb lengthening is specifically evaluated, Lumpkin et al., using a rat distraction osteogenesis model, demonstrated that as much as 10% of body

* Corresponding author: Nationwide Children's Hospital, 700 Children's Drive, Suite T2E-A2700, Columbus, OH 43205, USA.
E-mail address: christopher.iobst@nationwidechildrens.org (C. Iobst).

https://doi.org/10.1016/j.jposna.2024.100056
Received 11 January 2024; Accepted 27 March 2024
Available online 9 April 2024

weight may be lost during the distraction phase. In addition, they found that nutritional support dramatically increased the mineralized bone formed over the 20-day distraction period [5]. Many clinicians performing distraction osteogenesis in children have observed a stage during lengthening in which some children show signs of depression, insomnia, and anorexia/weight loss. While this has not been studied, such children seem to respond to antidepressants such as Amitriptyline.

All patients being considered for limb lengthening or reconstruction should have a pre-operative bone health evaluation and optimization. As many articles in this journal issue have described, vitamin D is crucial to bone health. The prevalence of vitamin D deficiency in pediatric limb lengthening and deformity patients has been found to be high, similar to other pediatric studies. Sax et al. measured vitamin D levels on the first post operative day and found 32% of their patients were vitamin D deficient and an additional 41% were insufficient compared to adult patients who were 33.3% and 30.2% deficient and insufficient respectively [6]. They suggested that identifying these patients pre–operatively may allow for vitamin D "pre–habilitation" to optimize bone health prior to limb lengthening procedures. Remarkably, there are no other publications that investigate the role of vitamin D in this patient population. Similar findings were found by Iobst et al. in their pre-operative limb reconstruction patient vitamin D screening with 30% deficient and 67% insufficient (unpublished data). While a substantial percentage of patients embarking on a limb lengthening journey may have inadequate vitamin D levels, it is unknown how this vitamin D deficiency affects the patient's ability to form regenerate bone. It is presumed that supplementing patients with vitamin D to obtain levels in the normal range should help improve the bone healing index (duration of time/centimeter of lengthening), but this remains unstudied. A multi-center investigation evaluating the effect of pre-operatively treating vitamin D deficiency should be performed.

Price et al. have identified other important nutrients for bone health and bone healing, such as calcium, magnesium, boron, silicon, inositol, and vitamin K [7]. Supplementing these essential elements of bone formation should be considered in all distraction osteogenesis patients. Although previously obtainable, there are currently few over-the-counter supplements that incorporate all these nutrients into one formulation. Even multi-vitamin formulations that are advertised as being specific for bone healing are often missing some or all of the critical mentioned micronutrients. One formulation that lists having magnesium, boron, silicon, and vitamin K is NATURELO Bone Strength (Naturelo, Bridgewater, NJ) although the amount of vitamin D in it may be somewhat small. A pediatric orthopedic surgeon, Dr. Chad T. Price, based on extensive literature research [7] developed a series of supplements called Silical 1 (contains vit D, Calcium, and Magnesium), Silical 2 (contains vit C, K, Silicon, Boron, L-arginine, and Inositol) and Silical Boost (contains vit C, E, B6, Zinc, and Selenium) that included what he felt to be the important nutraceuticals for optimizing bone healing. These products, inexplicably minus Silical Boost, are now manufactured and marketed by Dr. Don Colbert (Divine Health, https://shop.drcolbert.com/).

It is important to realize that malnutrition can be found in both underweight and overweight patients. Adequate access to healthy nutrition can be an issue for many families. Furthermore, even when healthy options are available, coaxing a child to consistently eat healthy provides an extra layer of difficulty. To our knowledge, there have not been any clinical studies directly evaluating the relationship between pre-operative nutritional status and regenerate bone formation in patients undergoing limb lengthening. Like the studies that found a high pre-operative rate of vitamin D deficiency, Iobst et al. found their pre-operative limb lengthening patients had pre-albumin levels that were insufficient 22% of the time and deficient 70% of the time (unpublished data). While there are many factors besides the pre-albumin level that determine the nutritional status of a particular patient, these low levels indicate that a nutritional deficit should be suspected and evaluated in all potential distraction osteogenesis patients. Despite the equivocal results demonstrated in neuromuscular spine surgery patients, pre-operative malnutrition is known to increase the risk of complications, length of stay, and costs of care in pediatric patients undergoing surgery [8,9]. Therefore, having a pre-operative nutritional assessment by a dietician or nutritionist seems appropriate for limb reconstruction patients.

Another pre-operative consideration for potential limb lengthening patients involves screening the patient's medications. Medications such as anti-coagulants, anti-seizure medications, loop diuretics, chemotherapeutic drugs, proton pump inhibitors, and anti-depressants can negatively affect bone healing [10]. In these situations, a discussion with the patient and their medical team should be arranged to determine if the medications can be temporarily stopped safely or if they can be replaced with alternatives.

Finally, pre-operative planning of the osteotomy can have an impact on the bone healing outcome [11]. The osteotomy should be planned at an area of healthy bone with adequate blood supply and soft tissue coverage. Increasing the osteotomy surface area for healing is also thought to be beneficial. Metaphyseal locations are preferred over diaphyseal when possible. Creating an oblique bone cut rather than a straight transverse cut is another potential method for increasing the surface area for healing. Professor Ilizarov emphasized the importance of minimally invasive corticotomy, stable fixation, a latency period, and gradual distraction (divided into small amounts over the course of the day). All of these are important for creating optimal regenerate bone in limb lengthening.

Post-operative setting

Most patients undergoing limb lengthening surgery get at least one single dose of prophylactic antibiotics to prevent deep infection. Often, they get longer (weeks) courses of oral antibiotics to treat pin site infections. While generally necessary, any course of antibiotics can negatively affect the gut flora. Microorganisms in the gut play an important role in regulating micronutrients, both in terms of facilitating the biosynthetic process and by controlling absorption into the blood stream [12]. A single dose of oral antibiotics has been shown to minimally affect the gut microflora [13]. However, a 5-day course of oral antibiotics can substantially affect the microbiome [14].

The post-operative period of limb lengthening and reconstruction is divided into 3 phases: (1) Latency – this represents the time from completion of surgery to the first planned adjustment of the bone position; (2) Distraction – the time from when adjustments to the bone position start until they are concluded; (3) Consolidation – the period of time from when bone adjustments are stopped until the regenerate bone is healed (Fig. 1). Typically, the duration of the latency phase is measured in days, the distraction phase is measured in weeks and the consolidation phase is measured in months. Strategies to improve bone formation during the distraction phase and accelerate bone healing during the consolidation phase would be clinically valuable. Much of the research in these areas, unfortunately, is still investigational with limited available clinical data. The final portion of this review will attempt to summarize the current methods being evaluated to improve the post-operative bone health for distraction osteogenesis patients.

The methods to improve bone formation and accelerate healing can be divided into 2 main categories: (1) externally applied forces/mechanisms and (2) internal manipulation of the bone healing process via medications or supplements. Multiple externally applied methods have been investigated to enhance bone formation and healing in distraction osteogenesis such as low-level laser therapy, extracorporeal shock wave therapy, low-intensity pulsed ultrasound, hyperbaric oxygen, transcutaneous application of CO_2, and pulsed electromagnetic fields [15–21]. There are some potentially encouraging results with each of these techniques, but further study is required as none of them seems to have demonstrated clear clinical benefit.

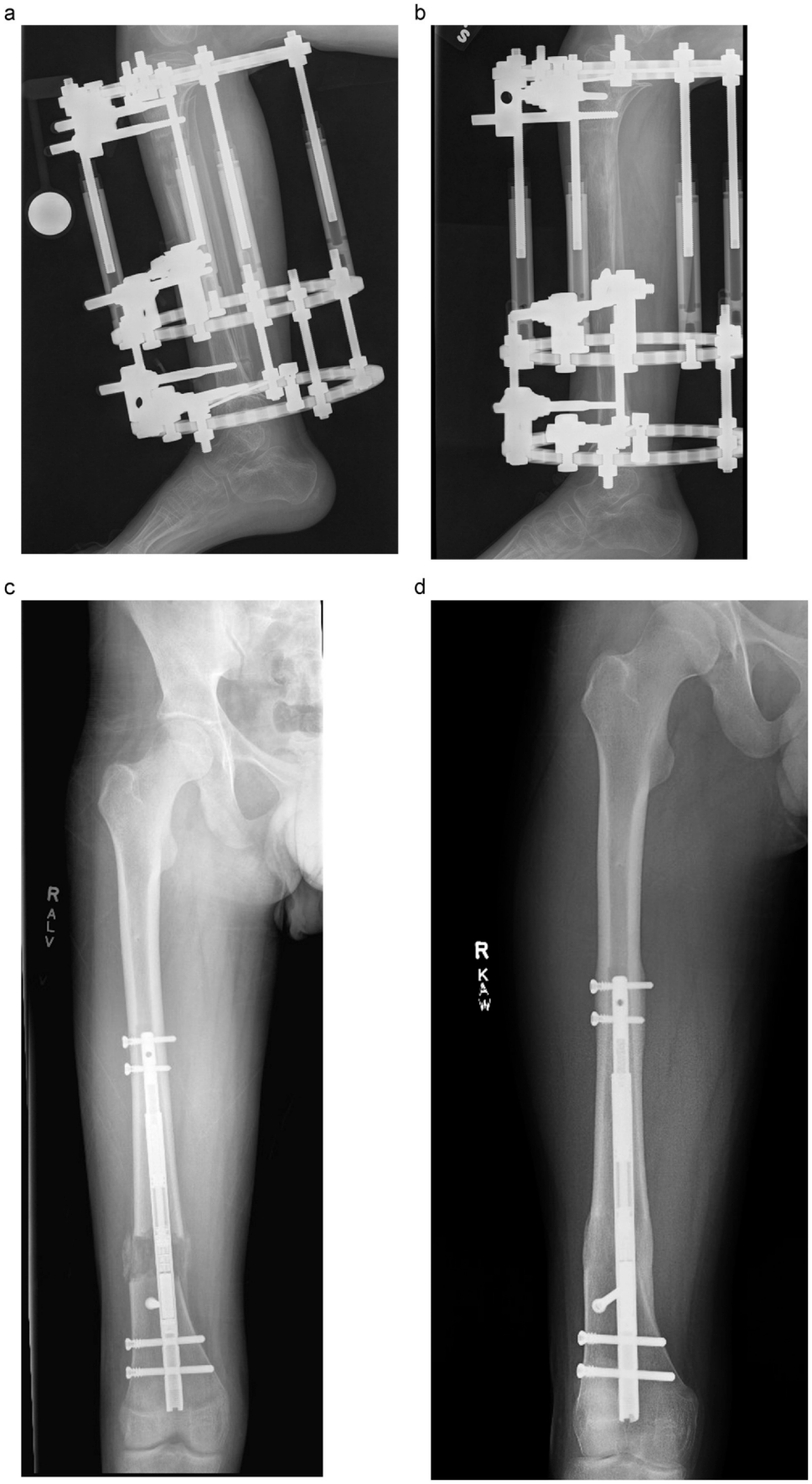

Figure 1. (a) Distraction phase during tibial lengthening with an external fixator. (b) Consolidation phase during tibial lengthening with an external fixator. (c) Distraction phase during femoral acute deformity correction and lengthening with an internal lengthening nail. (d) Consolidation phase during femoral acute deformity correction and lengthening with an internal lengthening nail.

Mechanical stimulation of the bone has also been attempted as a method to improve bone healing. Both the accordion technique and the reverse dynamization technique have been demonstrated to improve bone consolidation in animal models [22–25]. However, further study is required to identify the optimal timing of the maneuvers and the amount of micromotion necessary to obtain clinical benefit. Weight bearing after limb lengthening or reconstructive surgery as quickly as possible has been shown to be beneficial in both animal and clinical studies. Early regenerating DO tissue was able to respond to loading and weight bearing seemed to stimulate intramembranous ossification in a rat model [26]. A clinical study on internal lengthening nails found that earlier weight bearing accelerated the rate of healing during the consolidation phase [27].

While many of the medical methods to improve bone formation are still investigational, there are a few that have human clinical data. Bisphosphonates hinder bone resorption by directly acting on the function of osteoclasts, and also hinder the osteoblastic recruitment of osteoclasts. In a clinical trial conducted by Kiely et al., 7 patients with insufficient regenerate after limb lengthening with an external fixator received intravenous bisphosphonate treatment [28]. Six of the patients' fixators were removed without requirement for other intervention, which demonstrated a sustained and rapid improvement in local bone mineral density. This phenomenon probably represents an imbalance between the normal anabolic and catabolic processes that effect bone. If the catabolic process dominates (excessive osteoclastic activity), then bisphosphonates may be helpful. Several animal studies support this clinical finding. Pampu et al. assessed the effect of systemic application of zoledronic acid on the mineralization of newly formed bone, and their results showed that zoledronic acid can dramatically promote the new bone formation, which may potentially accelerate the consolidation period [29]. Akbulut et al. confirmed the effects of a single dose of 0.1 mg/kg or 0.2 mg/kg systemically administered zoledronic acid, when compared with the controls, and suggested this may be an effective strategy for promoting new bone maturation in rat femurs during distraction osteogenesis [30]. Although systemic administration of bisphosphonates has been proved effective in accelerating bone formation in distraction osteogenesis, potential complications, such as osteonecrosis of the jaw, nephrocalcinosis and gastrointestinal disorders should not be ignored [31]. The local application of bisphosphonates in distraction osteogenesis might help eliminate most complications caused by systemic administration while still accelerating bone tissue formation. Dundar et al. found that the local application of zoledronic acid could be safe and advantageous during the distraction osteogenesis consolidation period [32]. Alp et al. utilized a rate of 1 mm/day lengthening and locally injected low-dose alendronate in rabbit mandibles which provided the optimal new bone formation [33].

Endogenous human peptides and hormones such as adrenomedullin, melatonin, calcitonin gene-related peptide, and parathyroid hormone have been studied regarding their potential to influence bone healing [34–37]. While most of these studies are still investigational and involve animal models, there has been one clinical study involving Teriparatide (rhPTH) which is the active fragment of endogenous human parathyroid hormone. Wagner et al. enrolled 16 patients and concluded that teriparatide treatment during the consolidation period might double the mineralization rate of the regenerate [37]. These results suggest that teriparatide has the potential to shorten the consolidation period in patients.

Other investigational strategies have employed various concepts to enhance bone healing by adding certain nutrients, using antibodies, or manipulating genes. Strontium, an element that has been frequently used to treat osteoporosis, has an affinity for bone. It has been reported to hinder bone resorption and stimulate new bone formation in animal models. Taylor et al. found that strontium citrate effectively accelerated the formation of new bone in the rabbit distraction osteogenesis model [38]. Deferoxamine (DFO) is an angiogenic activator triggering the HIF-1α pathway through localized iron depletion. Donneys et al. found that the angiogenic effect of deferoxamine would improve bone regeneration by promoting the quality and quantity of bone and the number of osteogenic cells [39]. Therefore, they concluded that for the purposes of enhancing the bone regeneration abilities and augmenting the vascular response of mandibular distraction osteogenesis, this would be a relatively affordable and safe strategy [40]. As an active metabolite of dietary vitamin A, all-trans retinoic acid (ATRA) is involved in the regulation of various biological processes, such as cell proliferation, differentiation and migration. Weng et al. found that genes related to osteogenesis, including BMP2, Runx2, and ALP were all significantly up-regulated following ATRA-treatment [41]. They concluded that ATRA enhanced bone formation and consolidation and promoted osteogenic differentiation of rat bone marrow-derived mesenchymal stem cells during distraction osteogenesis in a rat model. These findings suggested that ATRA might be a promising medication for accelerating bone consolidation during distraction osteogenesis treatment in patients.

During bone formation, the activation of macrophages, neutrophils, and mast cells generate oxygen-derived free radicals. These free radicals increase the production of osteoclasts, leading to insufficient bone generation. Consequently, the application of antioxidants may be beneficial to inhibit the negative effects of oxygen free radicals in the process of new bone formation. Vitamin E is known for its recognized antioxidative properties. Alpha-tocopherol, a vitamin E derivative has been found to act as a biological antioxidant preventing lipid peroxidation caused by free radicals derived from free oxygen. The findings of the Akcay et al.' study suggested that systemic alpha-tocopherol administration during distraction osteogenesis may stimulate new bone formation and increase the number of vessels, osteoblasts, and osteoclasts in rabbits by quantitative and radiologic bone morphological evaluations [42]. Sclerostin is a glycoprotein that is only secreted by osteocytes. It interacts with the LRP5/6 receptor, thereby restraining the intracellular Wnt signaling pathway, resulting in a decrease in bone formation activity. Antagonizing sclerostin can promote bone formation. McDonald et al. demonstrated that sclerostin antibody treatment increased bone formation and promoted regeneration with higher strength and bone volume. Moreover, the optimal effects of sclerostin antibody treatment can be present in the latter stages of distraction osteogenesis [43]. Anti-sclerostin antibody has been shown to be more effective than bisphosphonates and teriparatide in promoting bone formation by Alzahrani et al. [44].

Local gene therapies of bone morphogenic protein (BMP) have been reported to induce sustained and relatively high levels of BMP production during distraction osteogenesis in rats [45]. Osteogenic growth peptide given intravenously enhanced bone formation in a rabbit distraction osteogenesis model [46]. Finally, locally applied nerve growth factor enhanced bone consolidation in a rabbit distraction osteogenesis model [47].

Conclusion

Although distraction osteogenesis may require the greatest anabolic demand on bone in all of orthopedics, there is a relative dearth of clinical research evaluating methods to improve and accelerate bone formation. Evaluating and optimizing the bone health of any potential patient is wise. Investigational research to shorten the bone healing time is plentiful but, to date, has not translated to clinically relevant or practical uses. There are multiple opportunities to perform meaningful research in this field and prospective multi-center studies concerning bone health should be developed to advance our understanding of this critical concept in limb lengthening.

Author contributions

Anirejuoritse Bafor: Writing – original draft, Writing – review & editing. **John E Herzenberg:** Writing – review & editing. **Christopher Iobst:** Conceptualization, Data curation, Supervision, Visualization, Writing – original draft, Writing – review & editing.

Declarations of competing interests

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Christopher Iobst reports a relationship with Smith and Nephew Inc that includes consulting or advisory, a relationship with Orthofix Medical Inc that includes consulting or advisory, a relationship with NuVasive Inc that includes consulting or advisory, a relationship with OrthoPediatrics that includes consulting or advisory. He is the *JPOSNA*® section editor for lower extremity. John E. Herzenberg reports a relationship with OrthoPediatrics that includes consulting or advisory, a relationship with NuVasive Inc that includes consulting or advisory, a relationship with Orthofix Medical Inc that includes consulting or advisory, a relationship with Smith and Nephew Inc that includes consulting or advisory and royalties, a relationship with OrthoSpin that includes consulting or advisory, a relationship with Wishbone Medical Inc that includes consulting or advisory. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Nakchbandi IA. Osteoporosis and fractures in liver disease: relevance, pathogenesis and therapeutic implications. World J Gastroenterol 2014;20(28):9427–38.
[2] Moe S, Drüeke T, Cunningham J, Goodman W, Martin K, Olgaard K, et al. Definition, evaluation, and classification of renal osteodystrophy: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int 2006;69(11):1945–53.
[3] Cross MB, Yi PH, Thomas CF, Garcia J, Della Valle CJ. Evaluation of malnutrition in orthopaedic surgery. J Am Acad Orthop Surg 2014;22(3):193–9.
[4] Lalueza MP, Colomina MJ, Bagó J, Clemente S, Godet C. Analysis of nuritional parameters in idiopathic scoliosis patients after major spinal surgery. Eur J Clin Nutr 2005;59(5):720–2.
[5] Lumpkin CK, Aronson J, Shen XC, Gao GG, Skinner RA, Badger TM. The impact of total enteral nutrition on distraction osteogenesis in a rat model. J Bone Min Res 1996;11(7):962–9.
[6] Sax OC, Remily EA, Mohamed NS, McClure PK, Herzenberg JE. Prevalence of vitamin D deficiency in pediatric limb lengthening and deformity patients. J Limb Length Reconstr 2021;7(2):114–8.
[7] Price CT, Langford JR, Liporace FA. Essential nutrients for bone health and a review of their availability in the average North American diet. Open Orthop J 2012;6:143–9.
[8] Andras LM, Gupta K, Skaggs DL, Stephan S, Illingworth KD. Do routine nutrition consults for neuromuscular scoliosis help the patient or just the rankings? Pediatrics 2021;147:838.
[9] Raval MV, Brockel MA, Kolaček S, Simpson KE, Spoede E, Starr KNP, et al. Key strategies for optimizing pediatric perioperative nutrition-insight from a multidisciplinary expert panel. Nutrients 2023;15(5):1270.
[10] Panday K, Gona A, Humphrey MB. Medication-induced osteoporosis: screening and treatment strategies. Ther Adv Musculoskelet Dis 2014;6(5):185–202.
[11] Alzahrani MM, Anam E, AlQahtani SM, Makhdom AM, Hamdy RC. Strategies of enhancing bone regenerate formation in distraction osteogenesis. Connect Tissue Res 2018;59(1):1–11.
[12] Thomas RL, Jiang L, Adams JS, Xu ZZ, Shen J, Janssen S, et al. Vitamin D metabolites and the gut microbiome in older men. Nat Commun 2020;11(1):5997.
[13] Johnson RC, Van Nostrand JD, Tisdale M, Swierczewski B, Simons MP, Connor P, et al. Fecal microbiota functional gene effects related to single-dose antibiotic treatment of travelers' diarrhea. Open Forum Infect Dis 2021;8(6):ofab271.
[14] Anthony WE, Wang B, Sukhum KV, D'Souza AW, Hink T, Cass C, et al. Acute and persistent effects of commonly used antibiotics on the gut microbiome and resistome in healthy adults. Cell Rep 2022;39(2):110649.
[15] Jauregui JJ, Ventimiglia AV, Grieco PW, Frumberg DB, Herzenberg JE. Regenerate bone stimulation following limb lengthening: a meta-analysis. BMC Musculoskelet Disord 2016;17(1):407.
[16] Abd-Elaal AZ, El-Mekawii HA, Saafan AM, El Gawad LA, El-Hawary YM, Abdelrazik MA. Evaluation of the effect of low-level diode laser therapy applied during the bone consolidation period following mandibular distraction osteogenesis in the human. Int J Oral Maxillofac Surg 2015;44:989–97.
[17] Bereket C, Çakir-Özkan N, Önger ME, Arici S. The effect of different doses of extracorporeal shock waves. Exp Model Mandibular Distraction J Craniofac Surg 2018;29:1666–70.
[18] Dudda M, Hauser J, Muhr G, Esenwein SA. Low-intensity pulse ultrasound as a useful adjuvant during distraction osteogenesis: a prospective, randomized controlled trial. J Trauma 2011;71:1376–80.
[19] Mutlu I, Aydintug YS, Kaya A, Bayar GR, Suer BT, Gulses A. The evaluation of the effects of hyperbaric oxygen therapy on new bone formation obtained by distraction osteogenesis in terms of consolidation periods. Clin Oral Invest 2012;16:1363–70.
[20] Kumabe Y, Fukui T, Takahara S, Kuroiwa Y, Arakura M, Oe K, et al. Percutaneous CO_2 treatment accelerates bone generation during distraction osteogenesis in rabbits. Clin Orthop Relat Res 2020;478:1922–35.
[21] Luna Gonzalez F, Lopez Arévalo R, Meschian Coretti S, Urbano Labajos V, Delgado Rufino B. Pulsed electromagnetic stimulation of regenerate bone in lengthening procedures. Acta Orthop Belg 2005;71:571–6.
[22] Makhdom AM, Cartaleanu AS, Rendon JS, Villemure I, Hamdy RC. The Accordion Maneuver: a noninvasive strategy for absent or delayed callus formation in cases of limb lengthening. Adv Orthopedics 2015:1–8.
[23] Shen J, Ye X. Effect of "accordion" technique on bone consolidation during distraction osteogenesis. Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi 2018;32:558–67.
[24] Bafor A, Iobst CA, Samchukov M, Cherkashin A, Singh S, Glatt V. Reverse dynamization accelerates regenerate bone formation and remodeling in a goat distraction osteogenesis model. J Bone Jt Surg Am 2023;105:1937–46.
[25] Glatt V, Samchukov M, Cherkashin A, Iobst C. Reverse dynamization accelerates bone-healing in a large-animal osteotomy model. J Bone Jt Surg Am 2021;103(3):257–63.
[26] Radomisli TE, Moore DC, Barrach HJ, Keeping HS, Ehrlich MG. Weight-bearing alters the expression of collagen types I and 11, BMP 2/4 and osteocalcin in the early stages ofdistraction osteogenesis. J Orthop Res 2001;19:1049.
[27] Bafor A, Duncan M, Iobst CA. Early weight-bearing accelerates regenerate bone mineralization: a pilot study comparing 2 postoperative weight-bearing protocols following intramedullary limb lengthening using the pixel value ratio. Strateg Trauma Limb Reconstr 2020;15:74–8.
[28] Kiely P, Ward K, Bellemore C, Briody M, Cowell J, C T, Little DG. Bisphosphonate rescue in distraction osteogenesis. J Pediatr Orthop 2007;27:467–71.
[29] Pampu AA, Dolanmaz D, Tüz HH, Avunduk MC, Kisşnisşci RŞ. Histomorphometric evaluation of the effects of zoledronic acid on mandibular distraction osteogenesis. Rabbits J Oral Maxillofac Surg 2008;66:905–10.
[30] Akbulut Y, Gul M, Dundar S, Ozcan EC, Ozercan IH, Bozoglan A, et al. Evaluation of effects of systemic zoledronic acid application on bone maturation in the consolidation period in distraction osteogenesis. J Craniofac Surg 2021;32:2901–5.
[31] Liu Z, Liu Q, Guo H, Liang J, Zhang Y. Overview of physical and pharmacological therapy in enhancing bone regeneration formation during distraction osteogenesis. Front Cell Dev Biol 2022;10:837430.
[32] Dundar S, Artas G, Acikan I, Yaman F, Kirtay M, Ozupek MF, et al. Comparison of the effects of local and systemic zoledronic acid. Appl Mandibular Distraction Osteogenes J Craniofac Surg 2017;28:e621–5.
[33] Alp YE, Taskaldiran A, Onder ME, Karahan S, Kocyigit ID, Atil F, et al. Effects of local low-dose alendronate injections into the distraction gap on new bone formation and distraction rate on distraction osteogenesis. J Craniofac Surg 2017;28:2174–8.
[34] Wang F, Kong L, Wang W, Shi L, Wang M, Chai Y, et al. Adrenomedullin 2 improves bone regeneration in type 1 diabetic rats by restoring imbalanced macrophage polarization and impaired osteogenesis. Stem Cel Res Ther 2021;12:288.
[35] Cikan I, Mehmet G, Artas G, Yaman F, Deniz G, Bulmus O, et al. Systemic melatonin application increases bone formation in mandibular distraction osteogenesis. Braz Oral Res 2018;32:e85.
[36] Jia S, Zhang SJ, Wang XD, Yang ZH, Sun YN, Gupta A, et al. Calcitonin gene-related peptide enhances osteogenic differentiation and recruitment of bone marrow mesenchymal stem cells in rats. Exp Ther Med 2019;18:1039–46.
[37] Wagner F, Vach W, Augat P, Varady PA, Panzer S, Keiser S, et al. Daily subcutaneous teriparatide injection increased bone mineral density of newly formed bone after tibia distraction osteogenesis, a randomized study. Injury 2019;50:1478–82.
[38] Taylor BA, Bezuhly M, Brace M, Carter M, Hong P. Effect of strontium citrate on bone consolidation during mandibular distraction osteogenesis. Laryngoscope 2017;127:E212–8.
[39] Donneys A, Deshpande SS, Tchanque-Fossuo CN, Johnson KL, Blough JT, Perosky JE, et al. Deferoxamine expedites consolidation during mandibular distraction osteogenesis. Bone 2013;55:384–90.
[40] Farberg AS, Sarhaddi D, Donneys A, Deshpande SS, Buchman SR. Deferoxamine enhances bone regeneration in mandibular distraction osteogenesis. Plast Reconstr Surg 2014;133:666–71.
[41] Weng Z, Wang C, Zhang C, Xu J, Chai Y, Jia Y, et al. All-trans retinoic acid promotes osteogenic differentiation and bone consolidation in a rat distraction osteogenesis model. Calcif Tissue Int 2019;104:320–30.
[42] Akçay H, Kuru K, Tatar B, Şimşek F. Vitamin E promotes bone formation in a distraction osteogenesis. Model J Craniofac Surg 2019;30:2315–8.
[43] McDonald MM, Morse A, Birke O, Yu NYC, Mikulec K, Peacock L, et al. Sclerostin antibody enhances bone formation in a rat model of distraction osteogenesis. J Orthop Res 2018;36:1106–13.
[44] Alzahrani MM, Makhdom AM, Rauch F, Lauzier D, Kotsiopriftis M, Ghadakzadeh S, et al. Assessment of the effect of systemic delivery of sclerostin antibodies on Wnt signaling in distraction osteogenesis. J Bone Min Metab 2018;36:373–82.
[45] Sun Y, Xu J, Xu L, Zhang J, Chan K, Pan X, et al. MiR-503 promotes bone formation in distraction osteogenesis through suppressing Smurf1 expression. Sci Rep 2017;7(1):1–10.
[46] Zhao Z, Shao L, Zhao H, Zhong Z, Liu J, Hao C. Osteogenic growth peptide accelerates bone healing during distraction osteogenesis in rabbit tibia. J Int Med Res 2011;39(2):456–63.
[47] Wang L, Zhou S, Liu B, Lei D, Zhao Y, Lu C, et al. Locally applied nerve growth factor enhances bone consolidation in a rabbit model of mandibular distraction osteogenesis. J Orthop Res 2006;24(12):2238–45.