Reverse Dynamization: A Novel Approach to Bone Healing

Vaida Glatt, PhD
Slobodan Tepic, DrSci
Christopher Evans, PhD

From the Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, Queensland, Australia (Dr. Glatt), Kyon AG, Zurich, Switzerland (Dr. Tepic), and the Rehabilitation Medicine Research Center, Mayo Clinic, Rochester, MN (Dr. Evans).

The authors' work in this area has been supported by the US Department of Defense (W81XWH-10-1-0888 and W81XWH-13-0324), the AO Foundation, Switzerland (S-08-42G), and the Vice-Chancellor's Research Fellowship of Queensland University of Technology, Australia.

Dr. Tepic or an immediate family member has received royalties from Ruetschi Technology; is an employee of Kyon and Scyon Orthopaedics; and has stock or stock options held in Akeso, Kyon, and Scyon Orthopaedics. Dr. Evans or an immediate family member serves as a paid consultant to or is an employee of Orthogen AG and TissueGene; has stock or stock options held in Aldabra, Orthogen AG, and TissueGene; has received nonincome support (such as equipment or services), commercially derived honoraria, or other non-research–related funding (such as paid travel) from Medtronic Sofamor Danek; and serves as a board member, owner, officer, or committee member of the Advanced Equine Research Institute. Neither Dr. Glatt nor any immediate family member has received anything of value from or has stock or stock options held in a commercial company or institution related directly or indirectly to the subject of this article.

J Am Acad Orthop Surg 2016;24: e60-e61

http://dx.doi.org/10.5435/JAAOS-D-16-00239

Julius Wolff (1836-1902) demonstrated the remarkable ability of the long bones to adapt to their mechanical environment. This property underlies the strategy of dynamization as a way to improve bone healing. Introduced by De Bastiani et al[1] in the 1980s, dynamization requires initial rigid stabilization of an osseous defect to allow the soft tissues to recover and bone healing to begin. With the first radiographic indication of callus, which usually occurs after approximately 3 weeks, stabilization is loosened in the axial plane so that load is progressively transferred to the regenerate to stimulate bone formation and maturation.

This article describes a novel strategy in which the defect is first stabilized at low axial stiffness, with subsequent increase in stiffness at the first signs of radio-opacity. We call this reverse dynamization.[2]

Reverse Dynamization Concept

The concept of reverse dynamization arose as a means of stimulating endochondral bone formation. We predicted that early exposure of the defect to loading would enhance the differentiation of mesenchymal progenitor cells into chondrocytes, a process accelerated by mechanical stimulation.[3] Such loading, however, threatens to impair endochondral ossification by disrupting the formation of blood vessels within the ossifying structure. For this reason, we proposed to increase the rigidity of fixation at the first radiologic signs of mineral deposition within the defect. Epari et al[4] subsequently published a theoretical paper supporting our postulates.

Experimental Evidence

First experiments used a rat femoral critical-size diaphyseal defect stabilized with an external fixator. The fixator was designed to allow the axial stiffness to be modulated while attached to a living animal.[5] Recombinant human bone morphogenetic protein-2 (BMP-2) was used to initiate healing. These studies confirmed that healing was accelerated and improved by reverse dynamization using initial low stiffness (114 N/mm) fixation, followed by reverse dynamization to a high stiffness fixator (254 N/mm) after 2 weeks of healing[2] (Figure 1).

In a subsequent publication,[6] we confirmed this phenomenon and began to define the stiffness parameters and BMP-2 dose requirements.

Next Steps

We are about to start exploring the effectiveness of reverse dynamization in a sheep tibial defect model[7] as a prelude to possible human clinical trials and veterinary applications. Meanwhile, the mechanism of action of reverse dynamization requires elucidation. As noted, it was originally proposed as a means of stimulating the endochondral process. However, in our first study,[2] we could detect no evidence of early chondrogenesis. Nevertheless, the subsequent study,[6] using a lower dose of BMP-2 and a wider range of stiffnesses, identified cartilage at the defect site. The mechanism may thus be subtle, possibly involving an effect on the production of inflammatory

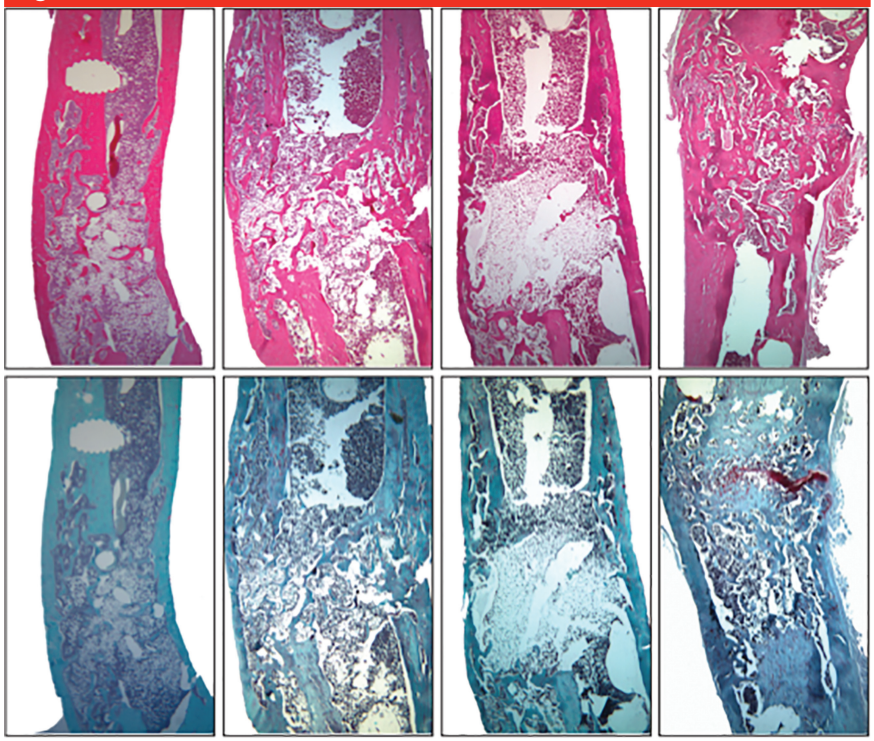
mediators and the activation of the transcription factor nuclear factor kappa-B (NF-κB).[8]

Experiments so far have used a large segmental defect model. The question is whether reverse dynamization will be effective in subcritical size defects and fractures. Pioneering studies by Hente et al[9] suggest effectiveness in the former. These investigators noted a dramatic increase in bone formation at the site of a 2-mm diaphyseal osteotomy in sheep under cyclic compression, but not distraction.

There are no preclinical data concerning the effectiveness of reverse dynamization in fracture healing, but Howard et al[10] recently published a pilot study in which a type of reverse dynamization was used to treat tibial fractures in humans. The outcomes were superior to those normally achieved using standard dynamization.

So far, the empirical evidence concerning reverse dynamization has come from studies using external fixators. Although it is possible to envision the use of sophisticated internal fixation devices for this purpose, external fixation has advantages of simplicity, affordability, and the possibility of removing the fixator once weight bearing is indicated, thus promoting maturation of the regenerate while preventing subsequent stress shielding.

Figure 1



Histologic appearance of defects 8 weeks after stabilization with low-stiffness (ExFixLow), medium-stiffness (ExFixMed), or high-stiffness (ExFixHigh) fixators or subjected to reverse dynamization RD). Low stiffness = 114 N/mm; medium stiffness = 185 N/mm; high stiffness = 256 N/mm. Stiffness increased from low to high after 2 weeks. Top row: hematoxylin-and-eosin staining; bottom row: safranin orange–fast green staining. (Reproduced with permission from Glatt V, Miller M, Ivkovic A, et al: Improved healing of large segmental defects in the rat femur by reverse dynamization in the presence of bone morphogenetic protein-2. *J Bone Joint Surg Am* 2012;94[22]):2063-2073.)

References

References printed in **bold type** are those published within the past 5 years.

1. De Bastiani G, Aldegheri R, Renzi Brivio L: The treatment of fractures with a dynamic axial fixator. *J Bone Joint Surg Br* 1984;66 (4):538-545.

2. **Glatt V, Miller M, Ivkovic A, et al: Improved healing of large segmental defects in the rat femur by reverse dynamization in the presence of bone morphogenetic protein-2. *J Bone Joint Surg Am* 2012;94 (22):2063-2073.**

3. Schätti O, Grad S, Goldhahn J, et al: A combination of shear and dynamic compression leads to mechanically induced chondrogenesis of human mesenchymal stem cells. *Eur Cell Mater* 2011;22: 214-225.

4. **Epari DR, Wehner T, Ignatius A, Schuetz MA, Claes LE: A case for optimising fracture healing through inverse dynamization. *Med Hypotheses* 2013;81 (2):225-227.**

5. **Glatt V, Evans CH, Matthys R: Design, characterisation and in vivo testing of a new, adjustable stiffness, external fixator for the rat femur. *Eur Cell Mater* 2012;23: 289-298.**

6. **Glatt V, Bartnikowski N, Quirk N, Schuetz M, Evans C: Reverse dynamization: Influence of fixator stiffness on the mode and efficiency of large-bone-defect healing at different doses of rhBMP-2. *J Bone Joint Surg Am* 2016;98(8):677-687.**

7. **Quirk N, Thoreson A, De la Vega RE, et al: Poster presentation. Mechanical characterization of a novel external fixator for dynamizing ovine osseous defects. Poster No. 2185. Presented at the Annual Meeting of Orthopaedic Research Society, Orlando, Florida, March 5-8 2016.**

8. Agarwal S, Deschner J, Long P, et al: Role of NF-kappaB transcription factors in antiinflammatory and proinflammatory actions of mechanical signals. *Arthritis Rheum* 2004;50(11): 3541-3548.

9. Hente R, Füchtmeier B, Schlegel U, Ernstberger A, Perren SM: The influence of cyclic compression and distraction on the healing of experimental tibial fractures. *J Orthop Res* 2004;22(4): 709-715.

10. **Howard CB, Leibergal M, Elishoov O, et al: Can changing the mechanical environment increase the speed of fracture healing? A pilot study in tibial fractures. *J Trauma Treat* 2013;2:176.**