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ORTHOPEDICS

(A POSTGRADUATE COMPANION)



2nd Edition

Volume 1

Highlights

- A Complete guide for Orthopedics PG Students which Covers all the Regions
- New Topics added – Mechanobiology and Metabolomics
- Included procedures – Arthroscopy and Arthroplasty Surgery
- Well-Written by experts of the field along with Clinical Photographs and Diagrams.

(Col) Samar Kumar Biswas

Foreword
KH Sancheti

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ORTHOPEDICS

(A Postgraduate Companion)

Second Edition

VOLUME 1

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CHAPTER

45 Mechanobiology in Orthopedics

OBJECTIVE

- Mechanobiology: Domains of Applicability

INTRODUCTION

Mechanobiology in orthopedics is a study of how mechanical or physical conditions regulate biological process in musculoskeletal regeneration. Skeletal regeneration is accomplished by a cascade of biological processes that may include differentiation of pluripotential tissue, endochondral ossification and bone remodeling.

It has been shown that all these processes are influenced strongly by local tissue mechanical loading, cyclic motion and the associated shear stresses cause self-proliferation and the production of large callus in the early phases of fracture healing.

For intermittently imposed loading in the regenerating tissue:

- Direct intramembranous bone formation in the areas of low stress and strain.
- Low-to-moderate magnitude of tensile strain and hydrostatic tensile stress may stimulate intramembranous ossification.
- Poor vascularity can promote chondrogenesis in an otherwise osteogenic environment.
- Hydrostatic compressive stress is a stimulus for chondrogenesis.
- High-tensile strain is a stimulus for net production of fibrous tissue.
- Tensile strain with a superimposed hydrostatic compressive stress will stimulate the development of fibrocartilage.

Finite element models are used to show that the patterns of tissue differentiation observed in fracture healing and distraction osteogenesis can be predicted from this fundamental mechanobiological concept.

In areas of cartilage formation, subsequent endochondral ossification normally will proceed, but it can be inhibited by intermittent hydrostatic compressive stress and accelerated by octahedral shear stress (or strain). Later, bone remodeling at the sites can be expected to follow the same mechanobiological adaptation rules as normal bone.

To consider the role of mechanobiology in fracture healing, it is useful to think about three overlapping phases. In the first phase, there is rapid proliferation of pluripotential tissue, which can differentiate into cartilage, bone or fibrous tissue, thereby forming the fracture callus. The proliferation and differentiation of tissue is under the influence of biological growth and differentiation factors and affected by epigenic chemical factors such as local oxygen tension besides being influenced strongly by the mechanical environment of regenerating tissue, although the interaction between the mechanical and biological factors in the differentiation process are unclear.

The second phase involves the endochondral ossification of cartilage formed at the fracture site. Although the endochondral ossification of skeletal anlagen is not mechanically loaded but the speed of endochondral ossification can be influenced by mechanical loading. The intermittent hydrostatic compressive stress will slow or stop endochondral ossification and intermittent octahedral shear stress or strain will accelerate the ossification.

Third phase in secondary fracture healing entails the remodeling of the formed intramembranous and endochondral bone. This bone remodeling is probably regulated by loading history in the same manner as bone during development and functional adaptation.

Continuous preosseous pluripotential tissue differentiation into cartilage, bone or fibrous tissue related to distribution of stress or strain of the local tissue environment takes part in the initial phase of skeletal regeneration in the long bone.

Then, by use of finite element of computer models, the spatial attempts of tissue differentiation expected in normal fracture healing and distraction osteogenesis are predicted. These patterns are compared with classic observation of fracture healing.

Comparing patterns of differentiation during tissue repair to prediction of mechanical environment within the mesenchymal tissue has led to development of number of hypothesis for mechanoregulated tissue differentiation. Theories on the relationship between the mechanics and biology were originally proposed in relation to fracture healing. These theories later developed into "mechanobiological algorithm", a finite set of rules that govern the effects of mechanical loading on stem cells and tissue; mechanobiology merges the older signs of mechanics with the newer and emerging discipline of molecular biology and genetics.

Mesenchymal stem cells (MSC) are not hematopoietic progenitor cells found in adult tissue. They possess an extensive proliferative ability in an uncommitted state and hold the potential to differentiate along the various lineage of mesenchymal origin in response to appropriate stimulus

Bone marrow is the most important source for MSCs. MSC have also been identified in differing other tissues such as adipose tissue, peritoneum, trabecular bone, synovium, skeletal muscles dental pulp and periodontal ligament. Quiescent MSC become mobilized

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during repair and remodeling through regulation by external chemical and physical stimulus that control their activation, proliferation, migration, differentiation and survival.

One key aspect in the mechanobiology of MSC is the modeling of cellular process such as cellular dispersal, proliferation, apoptosis, etc.

The MSC not only require time to differentiate but the differentiated cell types require time to synthesize and remodel new tissue. This purpose is based on the results of Richardson et al. who observed an exponential increase in stiffness during tibial fracture healing. They assume that the Young's modulus of all tissue within the fracture callus increases exponentially with time.

Pauwels who was the first to propose the hypothesis of mechanoregulatory tissue differentiation suggested that the distortional shear stress is the specific stimulus for development of collagenous fibers and the hydrostatic compressive force is the special stimulus for cartilage formation. When a soft tissue has stabilized, the environmental differentiation of MSC into osteoblast is favored leading to the formation of a bone. Based on quantitative analysis of clinical results of fracture healing, Peren (1979) proposed that the tissue differentiation is composed of tolerance to various tissue to strain (interfragmentary strain theory). Based on this theory tissue that ruptures or fails at a certain strain level cannot be formed in a region experiencing strains greater than this level, Pauwels expanded the concepts and proposed that local stress or strain history influences tissue differentiation overtime (mechanoregulation theory). The increase of compressive hydrostatic stress leads to formation of cartilaginous matrix, while increase of tensile strain leads to formation of connective tissue and fibrous matrix constituents. Fibrocartilaginous matrix is produced when there is a combination of increased compressive hydrostatic strain and increased tensile strength. Direct bone formation is permitted in regions exposed to neither significant compressive hydrostatic stress nor significant tensile strength provided there is an adequate blood supply. Preosseous tissue can be diverted down a chondrogenic pathway in region of low-oxygen tension.

MECHANOBIOLOGY: DOMAINS OF APPLICABILITY

Application of mechanobiology can be found in three main areas:

1. *In the development of new clinical therapies, e.g. in bone fracture healing or osteoporosis:* Different studies are reported in literature in which mechanobiological models are utilized to pursue this aim. Lacroix and Prendergast (2002) predicted the patterns of tissue differentiation during fracture healing of long bones. Shefelbine et al. (2005) simulated the fracture-healing process in cancellous bone.
2. *In the improvement of implant design:* With implants such as prosthesis, cells migrate up to implant surface and begin to synthesize matrix. But if micro motion is too high, bone will not form to stabilize the implant instead a soft tissue layer will form (Huskes, 1993; Prindergast 2006).

   A number of articles can be found in literature where mechanobiological models are utilized to predict the patterns of tissue differentiation at the tissue implant surface. Andreykiv et al. (2005) simulated the bone ingrowth on the surface of glenoid component. Moreo et al. (2009) developed a mechanoregulation algorithm that models the main biological interactions occurring at the surface of endosseous implants and is able to reproduce most of the biological features of most of the osseointegration phenomenon.
3. *In bone tissue engineering and regenerative medicine:* Appropriate biophysical stimuli are needed in bone scaffold in addition to nutrients and appropriate levels of oxygen, to favor an appropriate tissue differentiation process (Prindergast, 2009). A number of studies (Byrne et al., 2007; Milan et al., 2009; Olivares et al., 2009; Sanz Herrera et al., 2009) are reported in literature that, through a combined use of finite element method and mechanoregulation algorithms, described the possible patterns of the tissue differentiating within biometric scaffolds for tissue engineering (Boccacio et al., 2011).

   To focus on the first domain of applicability that is fracture healing or osteoporosis, we will take examples of two situations in human mandible osteotomized and submitted to distraction osteogenesis and proximal tibial corticotomy and submitted to distraction osteogenesis to show how mechanobiology can be used to predict the patterns of tissue differentiation in:

- Human mandible osteotomized and submitted to distraction osteogenesis to correct the geometry of the mandible, overcrowding, and malocclusion of teeth.
- Identical features of mechanobiological regulation and distraction osteogenesis are also observed in corticotomied proximal tibia and subjected to distraction osteogenesis at the corticotomy site at regulated rate of 1 mm per day (0.25 mm, 6 hourly) to achieve the closure of the gap at the fracture site.

The second situation is regrowth and remodeling process of the cancellous bone in osteoporotic vertebral fracture.

Mandibular symphyseal distraction osteogenesis (MSDO) is a common clinical procedure to modify the geometrical shape of the mandible for correcting problems of dental overcrowding and arch shrinkage. Such problems are usually solved by tooth extraction or expansion protocols. Such procedures are unstable and the results are unsatisfactory and likely to relapse. Mandibular distraction osteogenesis may solve transverse mandibular-deficiency problem. With this clinical procedure, the mandibular geometry is definitively changed so that the risk of relapse toward the original is avoided.

Proximal tibial corticotomy subjected to distraction osteogenesis (PTCDO) is also a common clinical procedure for treatment of open fracture tibia for simultaneous treatment of the fracture as well as the open wound with satisfactory end results as evidence-based clinical study and literature.

This osteotomy/corticotomy and distraction osteogenesis can be done in four stages:

Stage 1: Stage of Corticotomy/Osteotomy

Mandible is osteotomized/proximal tibia metaphyseal corticotomied and instrumented with a distraction appliance

Stage 2: Latency Period

Latent period (7–10 days) is waited after the surgery to facilitate the increased blood supply locally and beginning of formation of good bone callus.

Stage 3: Period of Distraction

The distraction device is progressively expanded with a well-defined rate for 7–10 days time period. Usual rate of distraction is 1 mm/day (0.25 mm, 6 hourly) till the fracture gap is closed in

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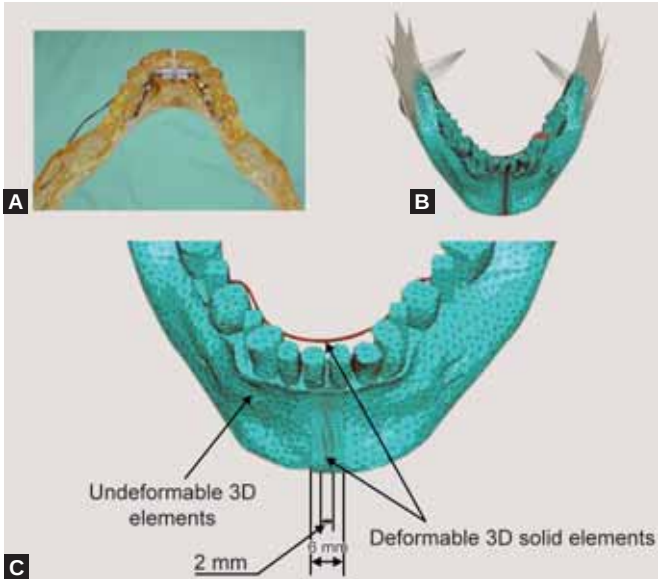

Figs. 1A to C: (A) Epoxy resin model of the osteotomized mandible with a tooth-borne device; (B) Mandible-distractor orthodontic device FEM model; (C) Details of the osteotomized region and of the tooth-borne device. (FEM: finite element method)

tibia with evidence of healing and correction of the geometry of the mandible with evidence of healing.

This is monitored by taking X-ray weekly. This will also control the over correction or under correction.

Stage 4: Stage of Maturation (Figs. 1 and 2)

The final stage is maturation period during which the patient is maintained in a rigid external fixation. The duration of this period usually is almost double the time taken for distraction in the treatment of fracture tibia. But the same time as for distraction in case of osteotomized mandible.

At the end of this period, for mandible more space is available in the inferior arch so that the overcrowded teeth can be repositioned in correct position.

In case of tibia, evidence of healing of fracture is detected clinically and radiologically, if satisfied for healing, the patient is allowed to do partial weight-bearing protected with patellar tendon bearing (PTB) brace.

The second stage is critical for successful MSDO and PTCDO. If the latency period is too short, a weak and insufficient callus will form and without a good callus not enough new bone may form and complications may arise such as fibrous union, non-union

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Figs. 2A to J: Distraction osteogenesis of tibia. Bone lengthening can be achieved through distraction osteogenesis using an Ilizarov external fixator. In this instance, an open distal tibial fracture resulted in a 3.7 cm segmental defect; the limb was acutely shortened, the wound closed primarily, and length gradually restored through a proximal corticotomy. This panel features a series of anteroposterior (AP) tibial radiographs demonstrating the 6 month process, and the final result a full year later. (A) Clinical image of the fractured limb stabilized with a circular frame after acute shortening of 3.7 cm; (B) AP radiograph immediately postoperative, with the proximal corticotomy minimally displaced; (C) AP radiograph of proximal tibia lengthening after 2 weeks of distraction; (D) AP radiograph of a proximal tibia lengthening at 4 weeks, with regenerate bone visible in the distraction gap; (E) AP radiograph of a proximal tibia lengthening at 6 weeks, as the gap slowly increases in size; (F) AP radiograph of a proximal tibia lengthening at 8 weeks, after length has been restored; (G) AP radiograph of a proximal tibia lengthening at 12 weeks, as the new bone gradually matures; (H) AP radiograph of a proximal tibia lengthening at 18 weeks, as the bone continues to consolidate; (I) AP radiograph of a proximal tibia lengthening at 26 weeks, shortly before the regenerate bone was solid enough to allow removal of the frame; (J) AP radiograph of the lengthened proximal tibia at 52 weeks, as the bone continues to strengthen and remodel. This regenerate bone will eventually become indistinguishable from surrounding normal bone.

in both MSDO and PTCDO; tooth loss and periodontal defect for MSDO (Coloney and Legas, 2003). On the other hand, too long a latency period may substantially increase the risk of premature bone union which can hinder the subsequent expansion process (distraction). Furthermore, the duration of latency period depends strictly on the age of the patient (Coloney and Legas, 2003).

In case of young children, the accelerated healing process allows clinical protocols with shorter latency period to be adapted, while in elderly patients as the healing process is slow, longer latency period is required.

The distraction period (Stage 3) is also critical.

Too fast a rate of expansion of appliance can lead to poor bone quality, within the distraction gap, partial union, fibrous union, atrophic non-union.

Conversely, too slow a rate can lead to immature consolidation. Hence, hindering the distraction process (Coloney and Legas, 2003).

Such issues have been investigated by developing a mechanoregulation model of a human mandible osteotomized or corticotomied proximal tibia subjected to distraction osteogenesis.

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