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Joint Loading Modality: Its Application to Bone Formation and Fracture Healing

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Abstract

Sports related injuries such as impact and stress fractures often require a rehabilitation program to stimulate bone formation and accelerate fracture healing. This review introduces a recently developed joint loading modality and evaluates its potential applications to bone formation and fracture healing in post-injury rehabilitation. Bone is a dynamic tissue whose structure is constantly altered in response to its mechanical environments. Indeed, many loading modalities can influence the bone remodeling process. The joint loading modality is, however, able to enhance anabolic responses and accelerate wound healing without inducing significant *in situ* strain at the site of bone formation or fracture healing. This review highlights the unique features of this loading modality and discusses its potential underlying mechanisms as well as possible clinical applications.

Keywords

joint loading; bone formation; fracture healing; strain; intramedullary pressure

INTRODUCTION

Bone is a metabolically active tissue capable of adapting its structure to varying biophysical stimuli as well as repairing structural damage through remodeling. Daily activities enhance its mechanical strength,^{1–3} and physical exercises such as swimming,^{4, 5} climbing,^{6, 7} jumping,^{8, 9} and running^{10, 11} can increase bone mass, density, and strength. Those activities or exercises are, however, mostly performed by healthy individuals^{12–15} and their efficacy depends on an individual's weight, muscle strength, and fitness level. For sports-related stress fractures caused by continuous overuse and fractures caused by a blow or a fall, athletes are often required to participate in a rehabilitation program. Those programs typically enhance bone remodeling in a manner which depends on the needs of the individual. Thus, various loading modalities have been developed to extend the loading effects to sports-injured athletes as well as elders and also astronauts.

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The results of many load-driven bone adaptation studies^{16–18} have focused on *in situ* strain at the site of bone formation.^{19–21} Not only loading experiments but also exposures to unloading by disuse or spaceflight²² support the role of *in situ* strain in preventing bone loss. However, recent animal studies using non-habitual loads administered by joint loading indicate that *in situ* strain is not an absolute requirement for load-driven anabolic responses. This review explains this novel joint loading modality. Herein is described its potential applications for enhancing bone formation and accelerating fracture healing as well as increasing bone length. Two proposed mechanisms underlying joint loading-induced responses are presented and future research directions are suggested.

LOADING MODALITIES

Functional loading modalities

Representative loading modalities, which have been extensively studied in the last 10 or more years, include whole-body vibration,^{23, 24} axial loading^{25, 26}, and bending.^{19, 27} Whole-body vibration applies oscillatory loads under 1 X G earth's gravity, and dynamically disturbs the mechanical equilibrium state of bone. The strain magnitude induced by whole-body vibration depends on both the size of the applied load as well as the loading frequency. Whole-body vibration can induce anabolic responses mostly in trabecular bone with, for instance, ~ 200 μ strain at 90 Hz loading frequency.²⁸ Axial loading and bending are generally applied to long bones such as ulnae and tibiae. Axial loading exerts principally longitudinal compression, while bending generates lateral compression and tension. Since ulnae and tibiae are naturally curved, axial loading induces not only longitudinal stress but also a bending effect. In tibiae, for instance, axial loading²⁹ and four-point bending^{30, 31} have been reported to induce a significant increase in bone formation mostly in load-bearing cortical bone.

Role of dynamic strain

Based on previous animal studies with various loading modalities, it is generally accepted that bone adaptation occurs in response to dynamic (rather than static) loading. The effect of loading represents a composite of critical determinants including strain magnitude, strain rate, and number of loading cycles and bouts.²⁰ In mouse ulna axial loading, for instance, dynamic strain above a certain threshold value (1000 – 2000 μ strain) is considered necessary to induce detectable bone formation. Furthermore, the optimal range of loading frequencies is 5 – 10 Hz.²⁶ In whole-body vibration, in contrast, a significantly higher loading frequency (above 1 kHz) is considered to be effective with smaller strain (< 100 μ strain).

JOINT LOADING MODALITY AND BONE FORMATION

Elbow, knee and ankle loading

Joint loading is the most recently developed loading modality. It employs non-habitual loads applied to a synovial joint such as the elbow, the knee, and the ankle. Unlike other loading modalities, it does not appear to depend on load-induced strain at a site of bone formation. Instead, loads are applied laterally to the epiphysis of the synovial joint and induction of bone formation is observed in the metaphysis and diaphysis of long bone.

Three forms of joint loading have so far been devised. Using a piezoelectric mechanical loader that can apply well-controlled loads at various waveforms, it has been shown in mouse studies that elbow loading,^{32, 33} knee loading,^{34–39} and ankle loading⁴⁰ are able to induce bone formation in the ulna, tibia and femur, and femur (Fig. 1).

Five noteworthy characteristics of joint loading

Joint loading offers several unique features for mouse studies. First, it requires smaller loads to induce bone formation than most of the other loading modalities. In mouse studies, for instance, axial loading needs ~ 2 N force for elevating bone formation in ulnae, while 0.5 N force is sufficient with elbow loading.

Second, joint loading is effective for inducing bone formation along the length of the entire long bone regardless of the longitudinal distance from the loading site. It has been shown that knee loading is able to induce bone formation not only in the distal diaphysis near the knee but also in the proximal diaphysis near the hip. Likewise, ankle loading is effective on the tibia along its length.⁴⁰

Third, compared to other loading modalities such as whole-body vibration, the number of required loading bouts is small. For instance, 1000 to 2000 bouts per day for 3 days are sufficient in mouse studies) with *in situ* strain of ~ 10 μ strain. According to the predicted relationship between strain and the number of daily loading cycles, whole-body vibration requires approximately 200,000 bouts for loading with 10 μ strain.

Fourth, although the periosteal cortical surface is more sensitive than the endosteal surface, both surfaces are responsive to joint loading.³⁷ It is, however, not well understood why the periosteal surface is more sensitive in most of the loading modalities (including joint loading) than the endosteal surface.

Fifth, a loading frequency of 2 – 15 Hz is effective, but existing data suggest that the optimal frequency differs among ulnae, tibiae, and femora.^{34, 35, 38} Geometry and dimension of each bone appear to affect frequency responses.

FRACTURE HEALING

Requirements for load-driven fracture healing

Although mechanical loading can non-invasively accelerate a process of fracture healing, a seemingly biphasic outcome with high sensitivity to loading intensity (stimulatory in low strain, and destructive in high strain) makes clinical applications somewhat restricted.⁴¹⁻⁴² The loading effects apparently depend on stress types (compressive, tensile, and shear) and strain magnitudes.⁴³⁻⁴⁹ The results of various animal studies support the notion that relatively low stress or strain promotes callus formation and increases bone strength.⁵⁰⁻⁵⁶ However, application of higher loads appears to result in a deleterious outcome.⁵⁰

Deformation and induced strain at the site of fractured bone are heavily affected by the method employed for fracture fixation, and healing phases.^{43, 57} The appropriate loading modality and its magnitude should be closely linked to the type of fracture.^{43, 58, 59} Furthermore, many loading modalities are often ineffective when fractures are immobilized by a cast.⁶⁰ Thus, a loading modality that does not require direct contact to the fracture site and induces small mechanical strain would appear to be well suited for accelerating fracture healing.

Healing of surgical wounds with knee loading

Because of its low-strain character, joint loading apparently satisfies the above requirements for fracture healing of long bones. As a preliminary trial, a healing process of surgically generated circular wounds was examined in the mouse tibia with and without knee loading. The results (based on μ CT imaging) were promising. Knee loading was able to accelerate closure of the surgical wounds and fasten the remodeling process.⁶¹ It would be interesting to know whether knee loading would be effective in fracture healing of a femoral neck, since the

femoral neck fracture represents a serious healthcare problem, especially in an aging population.

BONE LENGTHENING

Controversial loading effects

Longitudinal bone growth is the result of chondrocyte proliferation and its subsequent differentiation in the epiphyseal growth plates.^{62, 63} Although mechanical loading enhances bone formation and adaptation, its effect on bone length, more specifically, stimulatory or inhibitory influences on the growth plate, has been controversial. Some studies on physical exercises or mechanical loading report an increase in height of the growth plate,⁶⁴ while others show its reduction. Using axial loading of the ulna for rats, it has been demonstrated that longitudinal growth was suppressed in a dosage dependent manner.⁶⁵

Effects of unloading and knee loading

Lengthening of legs due to unloading during spaceflight has been documented. An important question is whether joint loading, which applies mechanical loads laterally and thereby stretches long bones longitudinally, can mimic the unloading effects of bone lengthening.^{34, 39} Preliminary data from a recent study using mouse long bones suggest that knee and elbow loading can lengthen the tibia and the femur, and the ulna and the humerus, respectively.

Differences in leg length above a normal variation of 5 – 15 mm potentially cause varying medical symptoms including hip and lower back pain, arthritis, and overuse injuries such as tendonitis.⁶⁶ In order to reduce lateral ground reaction forces acting predominantly on the short limb, a non-surgical treatment is of course wearing a shoe lift. In severe discrepancy cases, surgical treatments such as shortening the long leg and lengthening the short leg are conducted.⁶⁷ However, it is controversial how and when either of these invasive procedures should be performed. It has been proposed that insulin growth factor-1 (IGF-1) is effective to lengthen the tibia,⁶⁸ but clinical data suggest complexity of the effects of IGF-1. It was not yet been examined whether there is a linkage between the mechanical effects of joint loading and hormonal regulation through IGF-1.

POTENTIAL MECHANISMS

Strain gradient and intramedullary pressure

The most likely explanation for the effects of joint loading on bone formation is based on the following biomechanical considerations. Trabecular bone in the epiphysis is less stiff than cortical bone in the diaphysis,^{69, 70} and Young's modulus in the lateral direction is smaller than that in the axial direction.⁷¹ Therefore, lateral loads to the distal femoral epiphysis can be more effective than any axial loads to any other site in mobilizing interstitial fluid flow from the epiphysis towards metaphysis and the diaphysis. Since the epiphysis and the diaphysis are physically connected, the displaced fluid in the epiphysis could be transferred toward the metaphysis and the diaphysis. The following hypothesis is proposed: joint loading generates a steep strain gradient along the length of long bone and induces oscillatory alterations in intramedullary pressure. The pressure alterations in turn drive fluid flow in the lacunocanalicular network, which might cause shear stress to osteocytes (Fig. 2).^{36, 39}

Flow in a medullary cavity

The mechanism underlying acceleration of fracture healing with joint loading could be different from that for anabolic responses in intact bone. In intact bone, joint loading may cause cyclic alterations of intramedullary pressure,^{36, 37} which may affect interstitial molecular transport driven by pressure gradients.^{39, 72} In fractured bone, in contrast, pressure alterations would be

smaller since the damaged medullary cavity may not allow efficient build up of intramedullary pressure. One speculation is that molecular transports in the medullary cavity are activated in the fractured bone along with migration of bone marrow-derived cells. It has been reported that knee loading generates an oscillatory motion of micro particles in a glass tube connected to the surgical hole.³⁶ Further mechanical and cellular examinations are necessary to understand the interplay between the loaded epiphysis and the fractured diaphysis.

CONCLUSIONS

This review has explained that for sports related bone injuries joint loading is potentially an effective rehabilitation method for enhancing bone formation and accelerating wound healing in long bones. Besides the mechanisms underlying the observed load-driven responses, many basic and clinical questions remain to be answered: (a) Can anabolic responses be induced with absolutely no *in situ* strain in the diaphysis? (b) Does joint loading simulate migration and differentiation of bone marrow-derived cells in fractured bone? (c) Does joint loading reduce bone resorption in addition to inducing bone formation? (d) Can a similar loading modality be developed for strengthening the spine? And (e) Does joint loading provide a therapeutic effect on a jumper's knee or a runner's knee? Understanding the mechanisms of bone remodeling and fracture healing promoted by joint loading would likely answer the above questions and contribute to future treatments and therapies in sports medicine for promoting athletes' bone quality, and for accelerating healing of injured bones in an aging population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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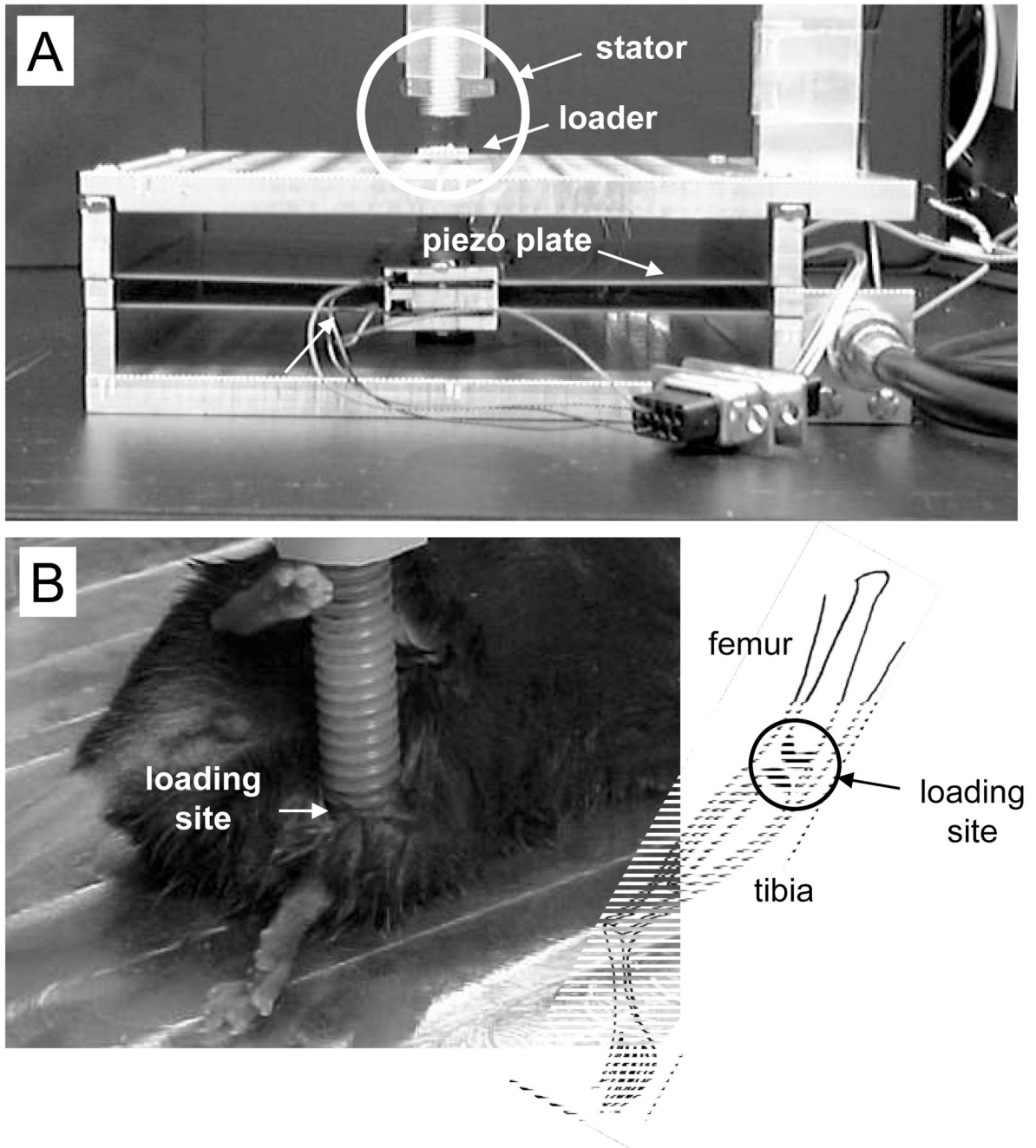


Figure 1. Knee loading apparatus used for the mouse model. (A) Piezoelectric mechanical loader showing location of mouse leg during joint loading session. Circled area is shown in (B). (B) Mouse leg during knee loading.

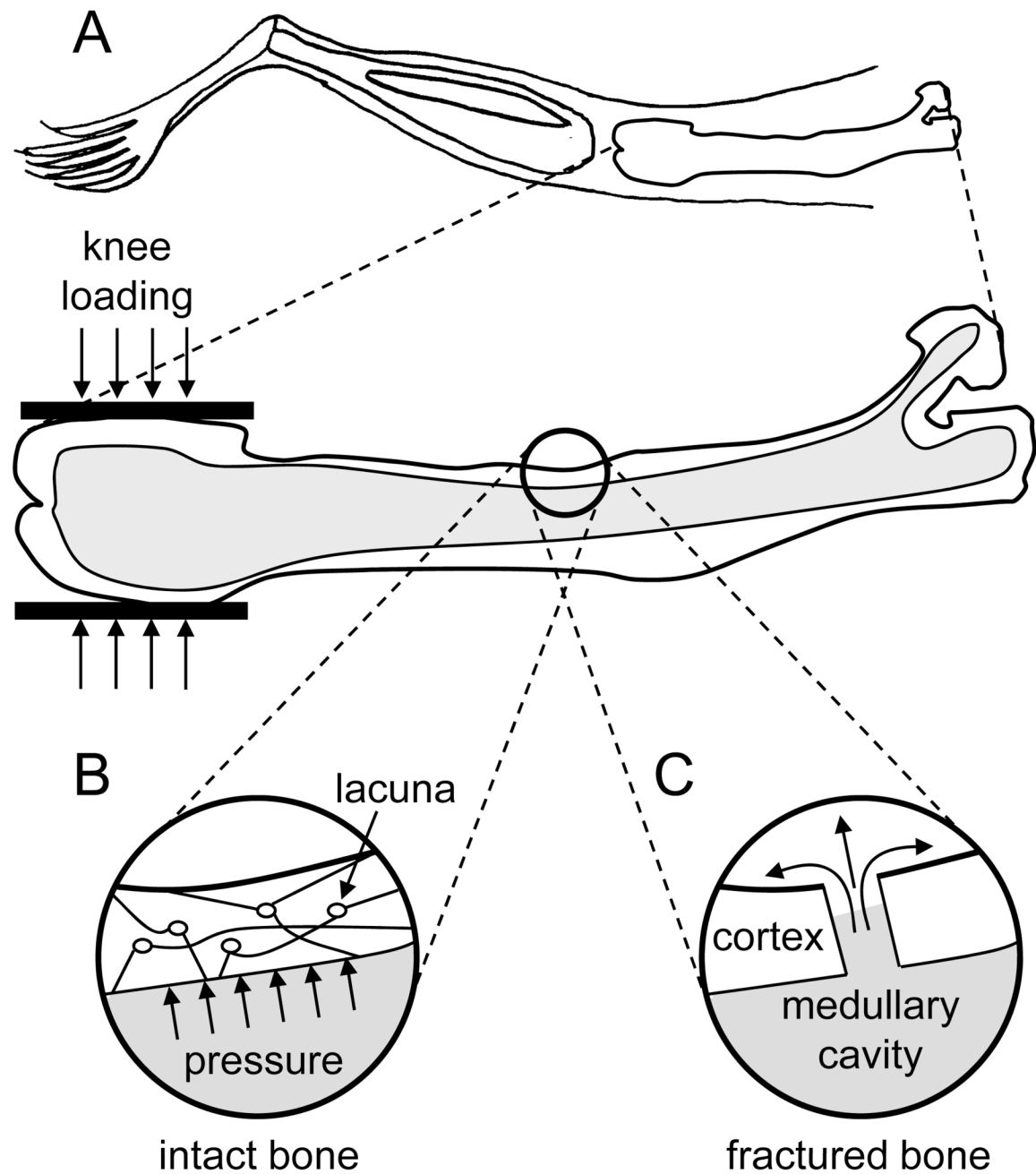


Figure 2. Potential mechanisms to account for the effects of joint loading. (A) Schematic illustration of a mouse femur under knee loading using the apparatus shown in Fig. 1. (B) Potential pressure increase in an intact bone cortex. (C) Potential fluid flow in a fracture bone cortex.