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Potential Applications of Pulsating Joint Loading in Sports Medicine

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Abstract

Since bone is responsive to mechanical loading, pulsating joint loading (PJL), which laterally applies oscillatory mechanical loads to joints, can be explored for preventative conditioning and therapeutic treatments. Herein the general features of PJL are reviewed, and its potential usage for sports medicine is discussed.

Summary—A recently developed pulsating-joint-loading modality is reviewed focusing on its unique features and potential usages.

Keywords

lateral loads; bone formation; wound healing; sports injury; molecular pathways

INTRODUCTION

Elite athletes frequently represent extreme cases of the need for bone strengthening therapies, and often are therefore given special attention, including extraordinary surgical interventions. For instance, tibial stress fractures (fatigue injuries) in high-level adolescent athletes are often difficult to treat (24). Similar needs are experienced by the general population, especially aging adults. Thus, the demand for bone strengthening therapies is enormous, and likely will increase as the intensity of athletic competitions escalates and as the population of developed countries ages. Bone loss due to osteoporosis, for instance, is predominantly observed in the elderly. Bone is a metabolically active tissue, and it should be possible, in principle, to devise strategies that exploit its natural anabolic and regenerative capacities. For injured athletes, geriatric patients, and astronauts options for the use of existing physical therapies, however, presently often are limited (10).

In this review we introduce a recently developed pulsating joint loading (PJL) modality and discuss its potential usage in sports medicine. PJL applies mechanical loads to a synovial joint, such as an elbow or a knee, and enhances bone formation and bone wound healing throughout long bones such as the ulna (23), the tibia (25–27), and the femur (27,28). Target-specific therapies with PJL might offer a new dimension in physical therapies with potential advantages over pharmacological interventions. Here we review the current understanding of its efficacy and discuss its possible biophysical mechanisms as well as its potential molecular signaling features.

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EXISTING APPROACHES FOR BONE-STRENGTHENING THERAPIES

Two primary traditional approaches for strengthening bone are pharmacological interventions and exercise routines (Table 1). Pharmacological agents include bisphosphonate pills, injection of parathyroid hormone, and application of selective estrogen receptor modulators. These agents offer several advantages: patient-friendly, in many cases easy to administer, and likely to be taken as prescribed for prolonged periods. Nevertheless, undesirable side effects may occur. For instance, the gastrointestinal drug-induced side effects of mucosal ulceration, gastrointestinal hemorrhage, diarrhea, and constipation have been observed (13). Only minor side effects such as occasional nausea and headache are known for the treatment with parathyroid hormone, but we do not fully understand possible long-term side effects of any of the existing drugs (15).

Exercise routines and mechanical stimulations include walking, jogging, running, swimming, and playing tennis as well as intense athletic training through weight lifting. Although exercise programs have long been proven to promote bone tissue growth (19), they are mostly directed towards injury prevention. Once a sports related injury happens, the active physical therapy is terminated and replaced by a procedure known as RICE (rest, ice, compression, and elevation). Few exercise programs are considered appropriate for severe injuries such as bone fractures. Furthermore, in elite athletes, or otherwise healthy young adults, rigorous exercise regimes are occasionally counterproductive by promoting stress fractures (16). Such side effects might conceivably include bone formation in unwanted areas or other negative consequences (2). Thus, there is a need to develop strategies that exploit the natural anabolic and regenerative capacities of bone which are suitable for injured athletes, geriatric patients, or astronauts with limited exercise tools.

PULSATING JOINT LOADING (PJL)

PJL in the form of knee, ankle, and elbow loading is a recently devised treatment modality, whereby bone strengthening is achieved through dynamic loads applied to a joint. Specifically, PJL loads are imposed laterally to the epiphysis of a synovial joint. Although the magnitude of loads is significantly smaller than other loading modalities such as ulna axial loading (21) and tibia four-point bending (7), PJL can induce bone formation and fracture healing in long bones. Bone histomorphometry using mice as an animal model has shown that PJL enables formation of new bone on the periosteal and endosteal surface of cortical bone in the ulna (elbow loading), tibia (knee loading and ankle loading), and femur (knee loading) (23,25–28). In each specific joint loading modality, induction of bone formation was observed in both the metaphysis and diaphysis of long bones. Figure 1 illustrates a loading experiment using a mouse, where well-controlled pulsating loads were applied using a custom-made piezoelectric mechanical loading device to the knee (covering the epiphyses of both the femur and the tibia). Typically, loads are given at loading frequencies of 1 – 20 Hz for 3–5 min per day. For mice, 0.5 N (peak-to-peak) force is sufficient to induce significant load-driven bone formation within a week.

Table 2 lists the advantages of PJL over other treatment modalities. First, PJL does not require direct contact with the site of bone formation or wound healing. Since its bone-strengthening effect is exerted throughout the length of a long bone, knee loading, for instance, can accelerate bone formation in both the distal diaphysis near the knee as well as the proximal diaphysis near the femoral neck (27). Healing of a surgical wound, generated in the diaphysis of the tibia, is accelerated by loads applied at the proximal epiphysis of the tibia with knee loading (Figure 2). Second, the apparatus for clinical use is inexpensive since pulsating loads at a frequency in the order of 1 to 10 Hz can be achieved with small, commercially available portable motors. Third, the procedure is non-invasive and no surgical intervention is needed. Fourth, PJL-based

therapy is likely to receive good compliance from patients because of its brief daily treatment duration (typically a few minutes) and small strains (less than 100 microstrains at the site of injury or wound healing). Fifth, PJL induces few side effects since applied loads are significantly smaller than weight-based training and no administration of chemical agents is required.

BIOPHYSICAL MECHANISM OF PJL

The biophysical mechanisms generated by PJL are different from most of the existing loading modalities, such as whole-body vibration (17), axial loading (21), and bending (7). Although all modalities require dynamic load application for efficient bone strengthening (8), PJL seems to eliminate the requirement for exceeding a strain threshold at the site of bone formation (25,26,28). This is probably because PJL effectively induces a pressure gradient throughout a long bone and this gradient establishes a remote communication link between the site of loading in the epiphysis and the site of bone formation in the metaphysis as well as in the diaphysis (30).

Based on several key features summarized in Table 3, the following working biophysical model is proposed: cyclic deformation of the epiphysis alters pressure in the medullary cavity and this pressure gradient induces fluid flow in the metaphysis and the diaphysis (Figure 3). Two types of fluid flow are conceivable: fluid flow in the lacuno-canalicular network in a porous bone matrix, and fluid flow in the bone medullary cavity. Flow in the lacuno-canalicular network is termed “interstitial fluid flow.” It is thought to produce dynamic flow shear to osteocytes housed in lacunae. Interstitial fluid flow is assumed to be driven by load-induced cyclic pressure alterations. Flow in the medullary cavity is thought to be induced in response to a bone wound that acts as a pressure sink. This flow is assumed to promote migration of bone-marrow derived cells including hematopoietic stem cells, mesenchymal stem cells, and endothelial progenitor cells. Their load-driven recruitment towards the site of the wound is proposed as the basis of accelerated healing.

Optimizing PJL-based therapies for sports injuries with regard to intensity and frequency, duration of rest/recovery periods may differ depending on the site and size of injury. That is, the distribution of intramedullary pressure routes might vary depending on the nature of the injury.

POTENTIAL MOLECULAR PATHWAYS INVOLVED IN PJL

In parallel with efforts directed towards elucidating the biophysical mechanisms of PJL, it is necessary to understand the molecular mechanism of action. Several cell types are likely involved in the PJL distance effects: chondrocytes in the growth plate, bone marrow-derived cells in the bone cavity, osteoblasts and osteoclasts together with cells in muscles, and the vascular system. Understanding how the activities of those diverse cell types are coordinated in response to PJL will require extensive gene expression research. Since the action of PJL is remote from the site of application, it is likely that some type of interstitial molecular transport and signaling is driven by the pressure gradient in the medullary cavity, but exact identities of biophysical mediators are yet to be understood.

Despite our lack of complete knowledge of the landscape of molecular pathways, some of the biochemical pathways activated within minutes of mechanical stimulation are known. First, mitogen-activated protein kinases (MAPKs) such as extracellular signal-regulated kinase 1/2 (ERK1/2), p38 MAPK, and Jun N-terminal kinase (JNK) are activated in osteoblasts in response to shear stress induced by fluid flow (22). Osterix, one of the critical transcription factors for bone development is induced by p38 MAP kinase. Furthermore, upregulation of type I collagen is mediated by ERK1/2 and JNK (22). Consistent with the predicted role of

interstitial fluid flow, the Wnt/β-catenin pathway in osteocytes has been proposed to mediate load-driven bone formation by crosstalk with the prostaglandin pathway and a suppression of negative regulators such as Sclerostin (Sost) and Dickkopf 1(Dkk1) (3).

Second, expression of peroxisome proliferator-activated receptor gamma (PPARγ), is downregulated by mechanical stimulation (11). PPARγ is a stimulator of adipocyte proliferation and a suppressor of differentiation of osteoblasts. Therefore, its down regulation seems to favor promotion of osteogenesis over adipogenesis. Our recent *in vitro* experiment using mouse C57BL/6 (MC3T3 E1) osteoblast-like cells, as well as primary mesenchymal stem cells isolated from mice, shows that fluid flow at 10 dyn/cm^2 for 1h significantly reduces the messenger ribonucleic acid (mRNA) level of PPARγ (unpublished observation, January 2008).

Third, previous studies have reported that expression of bone morphogenetic proteins (BMPs) and insulin-like growth factors (IGFs) are elevated in response to mechanical loading (12). The molecules are anabolic and their expression is at least in part mediated by transforming growth factor β (TGFβ) and/or phosphoinositide 3-kinase (PI3K) pathways. Taken together, molecular signaling pathways, which are potentially involved in PJL, include MAPK, PPAR, BMPs, IGFs, TGFβ, and PI3K. The detailed role of the molecules in PJL has yet to be investigated.

CONCLUSIONS AND PERSPECTIVES

In conclusion, existing animal studies support the notion that PJL offers a novel load-driven therapy for strengthening bone and accelerating healing of injured bones. Future research should be directed at evaluating the efficacy of PJL for strengthening long bones of athletes and healing of various sports-related injuries including trauma and overuse injuries in the tibia, femur, ulna, and humerus. A prototype PJL loader which could be effective for human use is being designed in our laboratory as a first attempt to develop a portable apparatus for astronauts in conditions of microgravity. However, no clinical data have been collected. In parallel with further development of a user-friendly device, evaluation of loading conditions suitable for individual sports injuries needs to be conducted.

Regarding biophysical and molecular mechanisms which drive PJL effects, intriguing questions include: (a) Is the loading frequency of 2–20 Hz employed in animal studies suitable for human use? (b) Knowing that tibial stress fractures (a common form of overuse injury) are occasionally difficult to treat, which is more effective for their healing, ankle loading or knee loading (Figure 4)? (c) Does administration of either IGF or TGFβ share the same molecular pathway as application of PJL? More specifically, would simultaneous application of PJL, and, for example IGF1, be more effective than either treatment alone? (d) Is PJL effective for healing injuries not only in long bones but also in joints such as ankle sprains and knee inflammation?

Understanding more about the physical and molecular features of bones and joints will contribute to the development of load-driven strategies for bone strengthening and injury healing.

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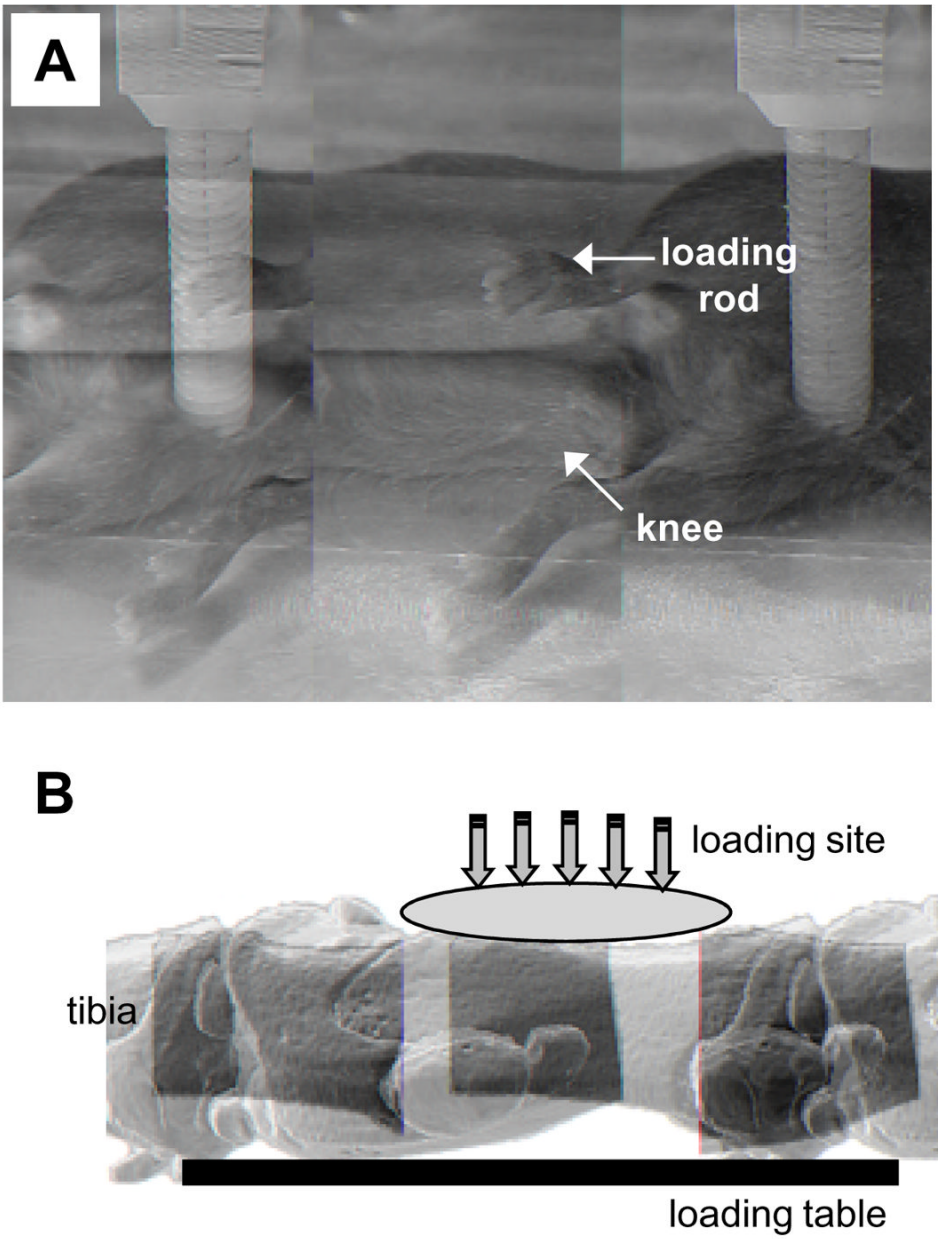

Fig. 1.
Configuration of the pulsating joint loading as designed for use on model laboratory animals (*e.g.*, mouse). A. Setting up knee loading with a mouse. B. Micro computer tomography image of the mouse knee.

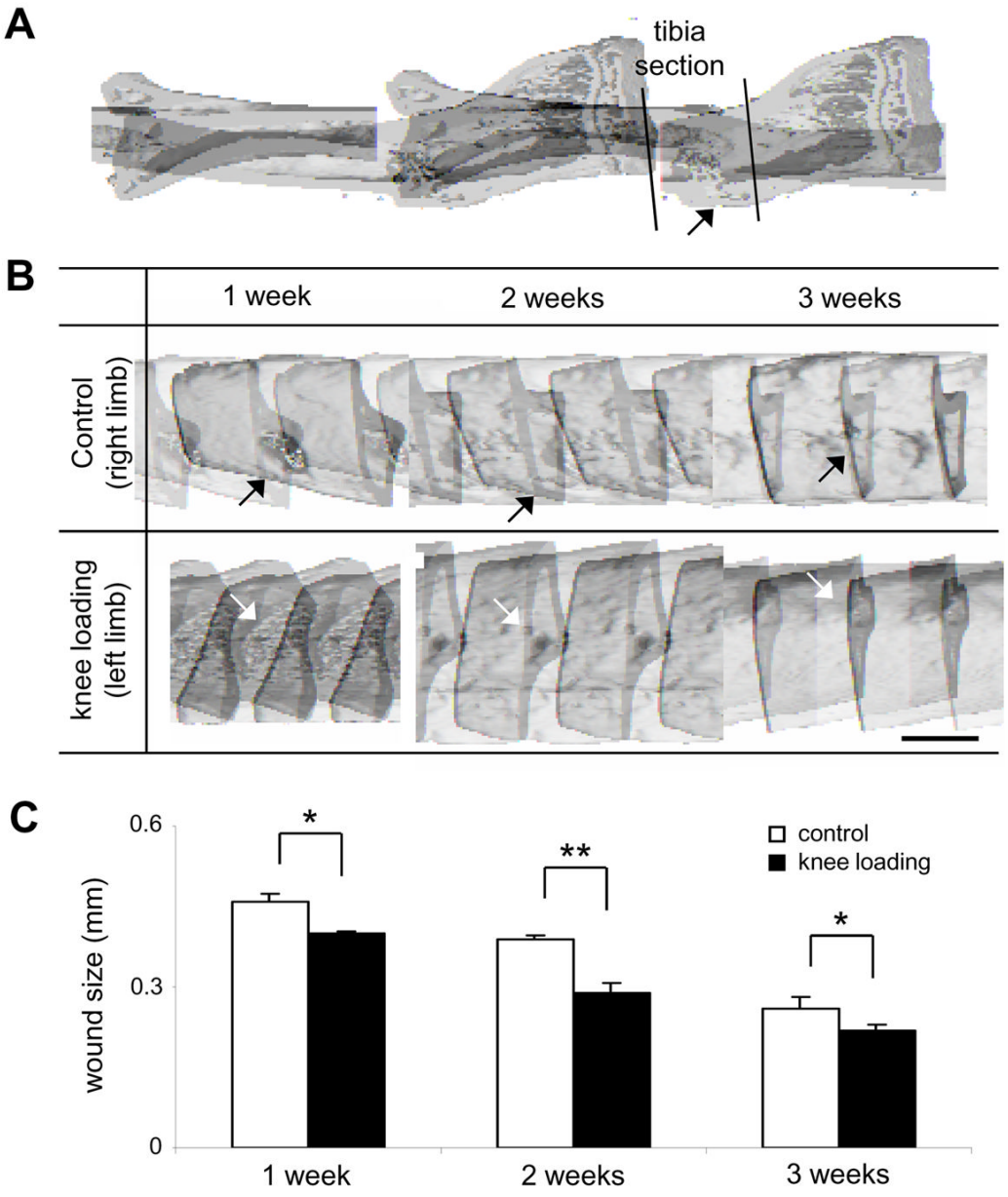

Fig. 2.

Micro computer tomography images of surgical wounds in the mouse tibia. A. Mouse tibia with a surgical wound. B. Healing of the surgical wound with and without knee loading. The tibia section was analyzed at 1, 2, and 3 weeks after surgery. The arrows indicate the positions of surgical wounds. Bar = 1 mm. C. Closure of the surgical wound with and without knee loading. The single and double asterisks indicate statistical significance at $p < 0.05$ and $p < 0.01$, respectively.

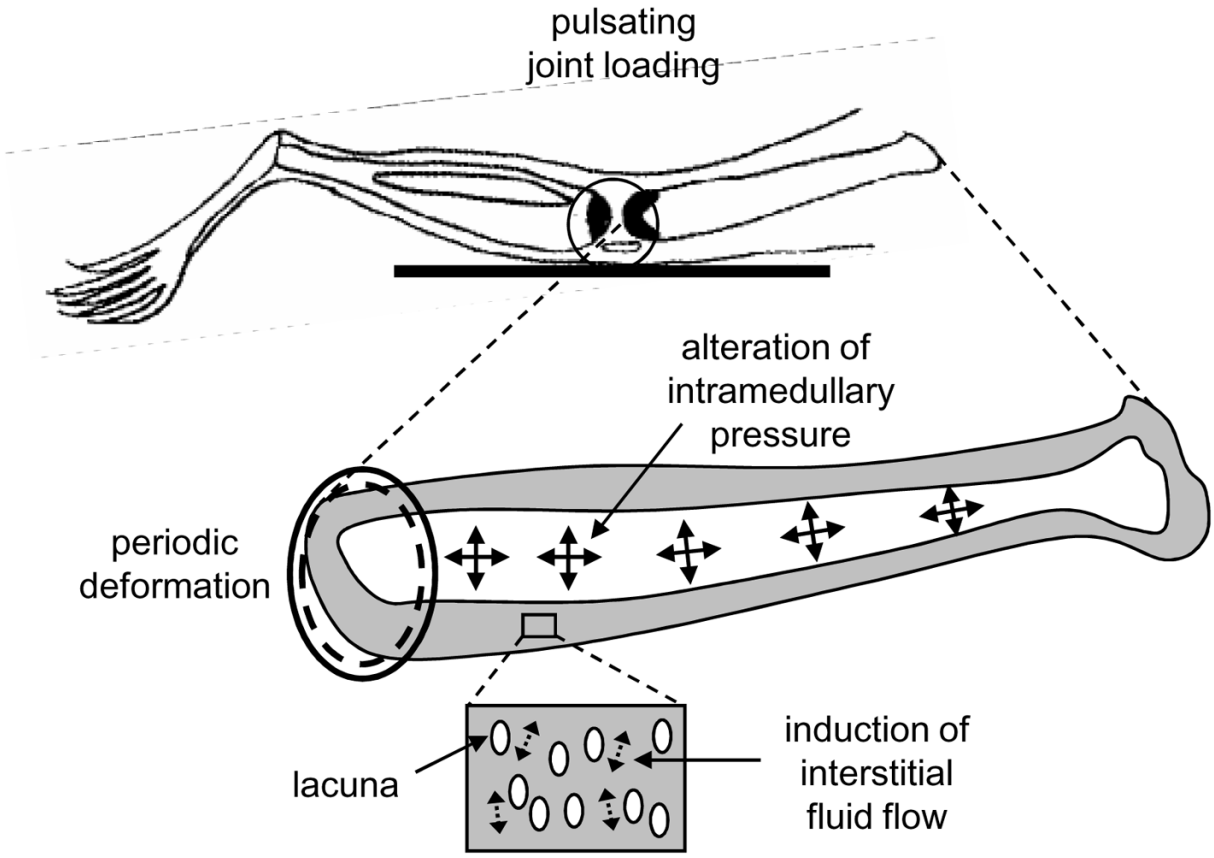

Fig. 3.
Schematic illustration of the proposed biophysical mechanism with knee loading. Pulsating joint loading induces periodic deformation in the epiphysis that drives alteration of intramedullary pressure in the medullary cavity and interstitial fluid flow in the lacunocanalicular network in the diaphysis.

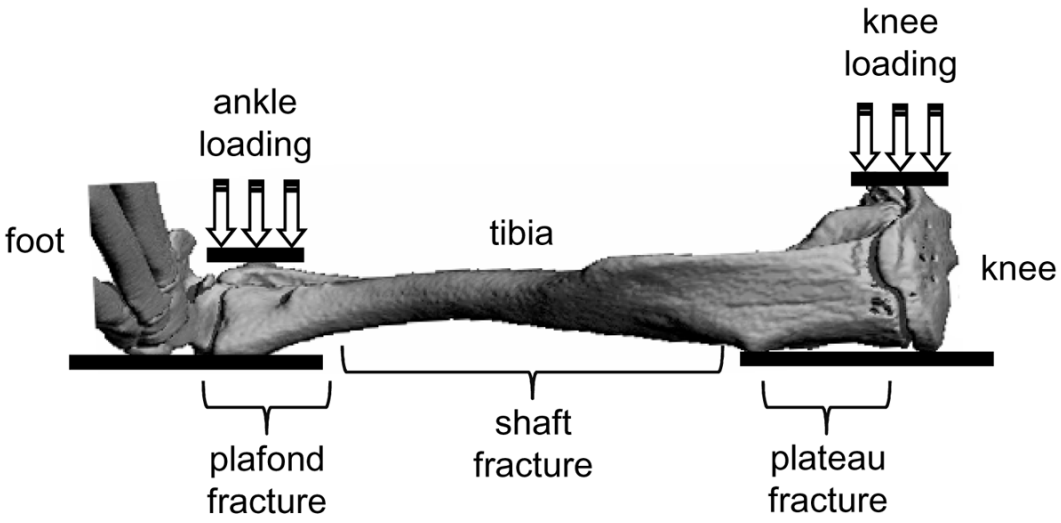

Fig. 4.
Schematic illustration of ankle loading and knee loading using a tibial fracture model.

TABLE 1

Examples of traditional bone-strengthening therapies

	Sample Treatment	Critique
Pharmacological interventions	Bisphosphonate pill	Possible gastrointestinal side effects (13)
	Parathyroid hormone	Promising, but frequent injections required (14)
	Selective estrogen receptor modulators	Possible increased risk of venous thrombosis (5)
Exercise routines and mechanical loading	Rhythmic physical activity (*e.g.*, running)	Individual variation exists (6)
		Desensitization may develop (20)
		Special needs for geriatric patients (9)
	Intense athletic training (especially sport or site-specific, *e.g.*, tennis vs swimming)	Limited effectiveness for osteoporosis (1)
		Routines occasionally suprathreshold intensity, and diet regulated (reviewed in Borer (4))

TABLE 2

Potential advantages of pulsating joint loading as a therapeutic tool

Feature	Comment
Might eliminate need for direct contact with injury site	Should be effective for patients with cast-immobilized wounds
Expected to be relatively inexpensive	Noninvasive, thus surgical intervention circumvented
Treatment likely to receive full compliance from patients	Requires low levels of strain, at brief intervals
Minimum side effects	Important for elderly patients who are taking various medications

TABLE 3

Experimental approaches to understanding cellular and molecular basis of mechanotransduction stimulated by PJL

Manipulation	Comment
Surgical holes drilled near site PJL	PJL effects diminished, presumably by reducing intramedullary pressure (29)
Fiber optical pressure sensor measurements	Suggest intramedullary pressure increased by PJL (30)
Biomechanical/dye transport studies	Suggest load-driven fluid flow (18)

PJL indicates pulsating joint loading.