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Perspective

Mechanical Effects on the Skeleton: Are There Clinical Implications?*

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Abstract. The basic morphology of the skeleton is determined genetically, but its final mass and architecture are modulated by adaptive mechanisms sensitive to mechanical factors. When subjected to loading, the ability of bones to resist fracture depends on their mass, material properties, geometry and tissue quality. The contribution of altered bone geometry to fracture risk is unappreciated by clinical assessment using absorptiometry because it fails to distinguish geometry and density. For example, for the same bone area and density, small increases in the diaphyseal radius effect a disproportionate influence on torsional strength of bone. Mechanical factors are clinically relevant because of their ability to influence growth, modeling and remodeling activities that can maximize, or maintain, the determinants of fracture resistance. Mechanical loads, greater than those habitually encountered by the skeleton, effect adaptations in cortical and cancellous bone, reduce the rate of bone turnover, and activate new bone formation on cortical and trabecular surfaces. In doing so, they increase bone strength by beneficial adaptations in the geometric dimensions and material properties of the tissue. There is no direct evidence to demonstrate anti-fracture efficacy for mechanical loading, but the geometric alterations engendered undoubtedly increase the structural properties of bone as an organ, increasing the resistance to fracture. Like all interventions, issues of safety also arise. Physical activities involving high strain rates, heavy lifting or impact loading may be detrimental to the joints, leading to osteoarthritis; may stimulate fatigue damage leading to stress fractures; or may interact with some pharmaceutical interventions to increase the rate of microdamage within cortical or trabecular bone.

Keywords: Bone fracture; Cortical bone; Functional adaptation; Mechanical stress; Trabecular bone

Introduction

Relationships between the mechanical environment and the form of the skeleton have been recognized since the time of Galileo [1], documented by Roux [2], dominated by Wolff [3], described by Thompson [4], and revived by Frost [5]. Nevertheless, the mechanisms and pathways by which mechanical stimuli effect an adaptive response in the skeleton are still being actively pursued, and their ability to reduce the risk of fracture debated. The healthy skepticism surrounding this debate arises, in part, from the apparently modest influence of physical loading on the adult skeleton [6,7] and the unlikely occurrence that methods adopted in controlled loading studies would be applied in a clinical setting. There is no question, however, that bone mass declines precipitously when the skeleton is subjected to disuse or immobilization [8–10]. Moreover, efficacy of pharmaceutical intervention to increase bone mass often relies on interactions between metabolic and mechanical functions of remodeling. For example, new bone formation induced by an anabolic agent will not be retained in the skeleton, following withdrawal of the agent, unless antiresorptive therapy is begun [11]. These observations exemplify the clinical importance of the relationship between mechanical loading and skeletal competence. However, there are no randomized, controlled trials of increased physical loading that have included anti-fracture efficacy as an end-point. One way to approach

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this issue is to critically analyze applied mechanical loads as an intervention using similar clinical criteria to those adopted for pharmaceutical interventions: that is, efficacy and safety.

The question of efficacy in this context is generally understood to mean anti-fracture efficacy. This implies that there is also a beneficial effect on those variables that influence bone fragility. For example, does increased mechanical loading influence both cortical and cancellous bone sites, can it prevent or reduce bone loss (modulate bone remodeling), can it activate modeling to stimulate new bone formation (or favorable adaptations to bone geometry), and can it increase bone strength, or resistance to fracture? Conversely, safety is less concerned with toxicity than with the potential for adverse events in bones and joints subjected to levels of mechanical loading above that experienced during normal activities.

This paper specifically examines skeletal adaptations to increased mechanical loading of the adult skeleton. In particular, it focuses on those adaptations affecting the structural properties of bone, and less on bone mineral density (BMD), the subject of many reviews on exercise and bone mass. Likewise, it will raise issues associated with safety, but not in an exhaustive fashion. It is not another review of exercise effects on bone mass because exercise and mechanical loading are not necessarily synonymous. The most direct evidence for skeletal adaptations to mechanical loading arises from controlled loading studies in animal models, but evidence from studies of physical activity will also be examined where appropriate.

Cortical and Cancellous Bone

When subjected to loading, the ability of bones to resist fracture depend on their mass, material properties, geometry and tissue quality. For example, for the same bone area and density, small increases in the diaphyseal radius effect a disproportionate influence on torsional strength of bone. Likewise, the elastic modulus and the shear modulus, measures of the intrinsic stiffness of a material in bending and torsion, are related to the cross-sectional geometry of a bone. Stiffness is an important property because it determines the amount of deformation engendered in a bone for a given applied load. In addition, the yield strength and ultimate strength of cortical and cancellous bone tissue are very highly correlated with bone stiffness [12]. The practical significance of this relationship is that an in vivo estimate of bone stiffness (e.g., from ultrasound measurement) may be a surrogate for bone strength [12]. The bending stiffness of a hollow cylinder such as bone is:

$$\text{Stiffness} = EI$$

where E is the elastic modulus and I is the areal moment of inertia of the cross-section about the axis of bending. In the case of a hollow circular cylinder, I represents the distribution of the bone material about the axis of bending and is given by:

$$I = \pi(r^4_o - r^4_i)/4$$

where r_i is the inner radius and r_o is the outer radius. A similar relationship exists for torsional loading except that the material property is denoted by the shear modulus, and the geometry by the polar moment of inertia.

There are two important points to note from these relationships. First, the elastic modulus and the geometry of the structure are equally important in determining the bending stiffness of the structure; and second, small increases in the radius of a bone's cross-section influence the moment of inertia (and therefore breaking load and stiffness) in a disproportionate fashion. The interaction between material and structural properties is important because the two parameters may vary independently in response to a given treatment. For example fluoride treatment at 50 ppm per day for 3 months decreased the intrinsic strength (ultimate stress) of bone in young rats, but it also increased the size of the femur such that ultimate bending load remained unchanged [13]. That is, the fracture resistance of the bones was retained, despite a significant degradation in their material properties. The bones achieved this mechanical maintenance by increasing their subperiosteal dimensions, *vis à vis* their moments of inertia, to compensate for the decline in the quality of bone material.

The pertinence of this discussion is that skeletal adaptations to mechanical loading typically involve modeling responses to effect favorable increases in the geometry, and hence the structural properties, of bone, independent of the material properties (Fig. 1). This contribution of altered bone geometry to fracture risk is unappreciated by clinical assessment using dual-energy X-ray absorptiometry (DXA) because it fails to

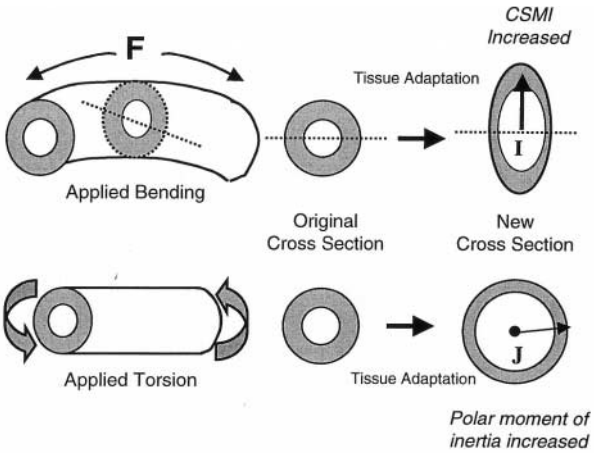

Fig. 1. Typical adaptations to long bone geometry to increase resistance to fracture in bending or torsion. Modeling on appropriate bone surfaces acts to increase the cross-sectional moment of inertia (*CSMI*) for bending, or the polar moment of inertia (*J*) for torsion. These changes can effect disproportionate increases in bending or torsional strength, independent of changes in material properties, but may be misinterpreted by dual-energy X-ray absorptiometry.

distinguish geometry and density. Nonetheless, the vast majority of loading studies employing physical activity in humans have relied upon measures of BMD derived from DXA to assess the adaptive response. This distinction is exemplified by results of a 6-month training program of the upper limb in 250 postmenopausal women [14]. DXA analysis showed no significant training effects in BMD at any of the sites measured, whereas significant increases in cross-sectional area and cortical bone mineral content (BMC) of the ultradistal radius were obtained by peripheral quantitative computed tomography (pQCT) [14]. Geometric properties such as distribution of bone mass, and length and angle of the femoral neck, can add information to bone mass and can be used to calculate stresses in bone tissue [15]. For example, geometric information is contained in the absorption curves generated by single and dual energy absorptiometry. Martin and Burr [16] demonstrated that cross-sectional moments of inertia can be calculated using single photon absorptiometry, and this has subsequently been applied to DXA [15,17].

Clinically, then, incorporation of geometric parameters relating to bone strength is already possible, and can provide estimates of whole-bone strength with greater validity and reliability than BMC or BMD alone [17–19]. For example, Beck et al. [17] developed Hip Strength Analysis for the proximal femur that incorporates principles of mechanical engineering into an analysis of bone mineral data acquired with conventional DXA systems. pQCT can also provide estimates of true bone density and geometry in the bones of the upper limb, providing a bone strength index which is based on the moment of inertia of the cross-section being scanned [18,19]. These methods have already been applied to estimate mechanical adaptations in human populations [15,20,21] and intervention studies [22].

Studies that employ experimental manipulation of mechanical loading demonstrate alterations in bone geometry that are consistent with the processes described in Frost's [5] mechanostat theory. That is, if bones are shielded from their normal mechanical usage, remodeling is stimulated and loss of bone mass ensues [10,23]. If loading is increased above a threshold, modeling is activated to alter bone geometry by modulating new bone formation or bone resorption at the appropriate surfaces [10,23–25]. In early studies, Lanyon and coworkers [24] increased strain in the radius of growing pigs by more than 35% by performing an ulnar osteotomy. This resulted in rapid periosteal deposition of bone. After 3 months the area of the intact experimental radius was equal to the combined area of the radius and ulna in the control limb, and compressive strains had returned to normal.

A more recent model from Lanyon's group provides an excellent illustration of typical adaptations that occur in long bones in response to bending [26]. This model applies compressive end-loads to the forearm of rats, inducing a bending moment in the ulna [26,27], a mode of loading analogous to that occurring physiologically. Short daily periods of dynamic loading, to a peak of 4000 microstrain over 10 days, increase modeling activity furthest from the axis of bending [26]. New bone formation increases along the lateral surface, and at the medial surface the normal resorptive activity is arrested and new bone formation is activated. At the cranial and caudal cortices (along the neutral axis) little adaptive activity is observed (Fig. 2). It is also important to note that differential modeling also occurs along the ulnar diaphysis. When compared with the unloaded contralateral ulna, increased periosteal apposition is observed in the loaded limb toward the distal end, but the mineral apposition rate is reduced toward the proximal end. That is, the whole bone adapts to the mechanical perturbation as a structure, highlighting the site specificity of adaptive changes.

Given the global nature of such adaptations, single observations from one small region of a long bone could easily be misinterpreted if viewed in isolation from the structural changes occurring throughout the bone [28]. Using unilateral sciatic neurectomy in rats, Lanyon [29] effectively illustrated that tibiae from limbs paralyzed for 16 months were straighter, and lacked the triangular cross-sectional profile of the contralateral bone (Fig. 3).

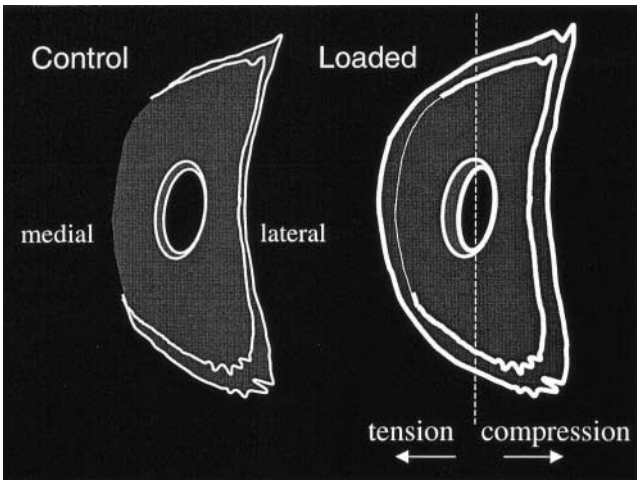

Fig. 2. Diagrammatic representation of new bone formation following bending of the right ulna (adapted from Mosely et al. [26]). Along the neutral axis (*dashed line*), new bone formation is least. Furthest from the axis of bending, bone resorption is halted and new bone formation initiated at the cranial surface, and bone formation is increased along the caudal surface.

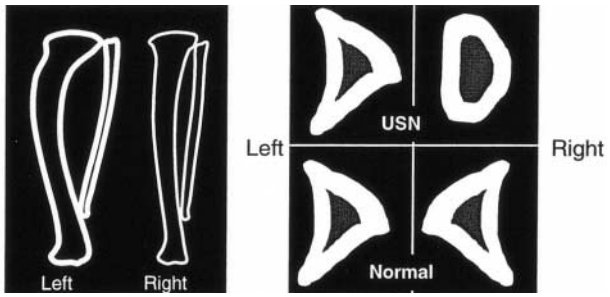

Fig. 3. After 16 months of unilateral sciatic neurectomy, rat tibiae were straighter (*left*) and lacked the triangular shape of their contralateral bone (*right*). (Adapted from Lanyon, [29].)

Radiographs also demonstrated the expected differences in bone density. Recent studies employing magnetic resonance imaging (MRI) to provide geometric information to supplement BMD are attempting to redress this design fault in studies of physical activity [30] and osteoporosis [31].

Can such adaptations be observed from physiologic loading associated with physical activity? Indeed, the femora from pigs subjected to walking exercise for 12 months illustrate that increases in the cross-sectional moment of inertia (CSMI) are associated with increased breaking load and energy absorbed to failure [32]. When normalized for the increased bone size, true bone density remained unaltered, as was the ultimate stress at failure. That is, the femur simply adopted a modeling response to alter its geometry, rather than its material properties. The cross-sectional area of the humerus in tennis players can also be as much as 35% bigger in the dominant arm of males and 28% bigger in females [33]. Such changes result from a combination of geometric changes at the periosteal and endocortical surfaces which, from more recent studies, result in increases to the CSMI of the distal diaphysis [34]. The biggest differences between dominant and nondominant humeri are observed in players who began their training before puberty [33], illustrating the importance of childhood physical activity to optimal bone development [7,35].

In cancellous bone, such as vertebrae, the ultimate breaking load in compression is related to the square of its apparent density multiplied by the cross-sectional area [36]. In lumbar vertebrae, this parameter accounts for 81% of the variation in failure load (Fig. 4). When compressed between the two adjacent vertebrae, increased trabecular thickness results from mechanically induced bone formation in the eighth caudal vertebrae of rats [37]. Increased trabecular thickness also occurs in the proximal tibial metaphysis of the overloaded limb following unilateral hindlimb immobilization for up to 28 weeks [10], (Fig. 5). In both models, increased trabecular thickness is accounted for by new lamellar bone formation onto the trabecular surface, and not just changes to the remodeling space [10]. By changing the

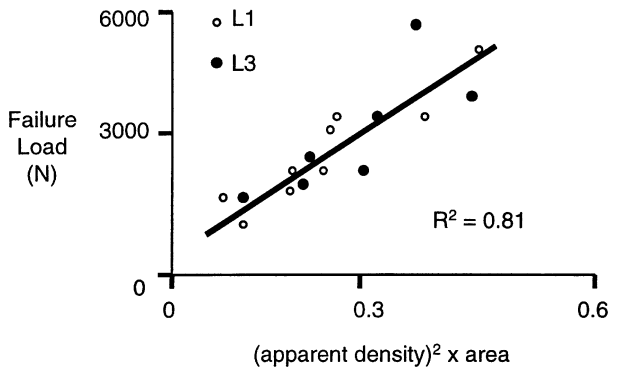

Fig. 4. Relationship between vertebral failure load and the product of average apparent density squared and cross-sectional area of trabecular bone within the vertebral body. (Adapted from Hayes and Gerhart [36].)

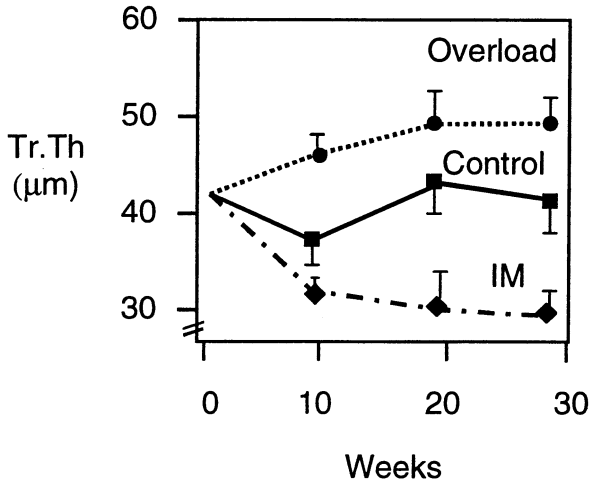

Fig. 5. Influence of unilateral hindlimb immobilization on trabecular thickness (*Tr.Th*) in the proximal tibiae of overloaded and immobilized limbs. (Adapted from Jee et al. [10].)

CSA and apparent density, such adaptations ultimately improve the resistance of cancellous bone to fracture.

Can such adaptations be effected in vivo with a mode of mechanical loading that might be feasible in the clinical setting? Preliminary studies suggest that trabecular bone volume of the proximal femora in sheep increased by 34% following low-magnitude, high-frequency mechanical vibrations for just 20 min per day over 12 months [38 Abstr.]. Sheep were exposed to a mechanical vibration each day at a frequency of 30 Hz by standing on platform through which the loading stimulus was applied. Such a change is clinically relevant, but is yet to be replicated in a human clinical trial [39 Abstr.]. If such an outcome can be substantiated with a clinical study of high quality, it offers a novel opportunity for combined mechanical and pharmaceutical intervention to increase bone mass with minimal physical effort – an advantage for aged or frail individuals.

While not exhaustive, these studies demonstrate that mechanical loading can activate a modeling response to influence bone geometry, independently of material properties. For bending and torsion of long bones, altered geometry can influence the cross-sectional moments of inertia, and new bone formation induced on trabecular surfaces increases the apparent density and cross-sectional area of cancellous bone. These adaptations affect the the structural properties of the bone, increasing the fracture load and stiffness. Although the discussion has focused on the structural adaptations to increased loading, adaptations to the material properties may also occur, for example, by increasing true bone density [37–39], or the orientation of the mineral crystals within the matrix [40].

Bone Strength: Anti-fracture Efficacy

If adaptations to structural and material properties are effected by increased mechanical loading, do they, in

fact, alter the risk of fracture? Surprisingly, these data are not available for controlled loading studies, and there are no randomized controlled trials of physical activity published with anti-fracture efficacy as an end-point. Prospective case–control studies show that among older community-dwelling individuals, greater physical activity is associated with a lower risk for hip fractures [41–43]. For example, in a study of 8600 postmenopausal women and 5049 men, those engaged in physical activity for between 30 min and 1 h per day reduced their risk of fracture by 50% for women and 60% for men [42].

The problem with these data is that they do not provide supporting evidence for the role of increased mechanical loading per se. This does not diminish their relevance in relation to physical activity and fracture risk. While exercise can reduce the rate of bone loss, it also improves muscle strength and postural stability, factors which themselves are independent contributors to the risk of fracture [44]. That is, their ability to reduce the propensity to fall can influence the risk of fracture independent of skeletal adaptations to mechanical loading.

Safety

Low-impact, low-intensity strength-building activities are unlikely to elicit significant adaptive responses in the adult skeleton [6,45,46]. They may, however, improve fitness and muscle strength, contributing to prevention of falls and a lower risk of fracture in the elderly [47–49]. From controlled loading studies in animals it is clear that osteogenic effects are maximized when loads are applied at high magnitudes or high loading rates [50–52]. *Ipso facto*, it follows that the most effective exercises for enhancing bone mass should be those that involve high strain rates, or impact loading, and this appears to be the case [44,45,53–55].

Unfortunately, activities that are associated with high strain rates, heavy lifting or impact loading are also associated with a risk for osteoarthritis (OA) [56–59]. Case–control data from the Framingham studies show that heavy physical activity is associated with incident OA in the knee joint [60]. Five hundred and ninety-eight subjects with no evidence of OA at baseline were re-evaluated 10 years later. At follow-up, the number of hours per day of heavy physical activity was associated with the risk of incident radiographic knee OA (odds ratio of 1.3 per hour). Those participating in heavy physical activity for 3 h or more per day increased their risk by as much as 13 times [60]. Clearly, there may be adverse side effects from simply extrapolating the data from controlled, experimental studies of mechanical loading to the design of exercise programs for maximizing bone mass.

Another consequence arising from repetitive mechanical loading of materials is the development of stress, or fatigue, failure. It is postulated that accumulation of microdamage in bone underlies the development of stress fractures, and plays a role in the increased fragility of bone associated with aging and osteoporosis [61]. The microdamage burden in bone is a function of the amount of damage that is produced, and the amount that is repaired through normal bone remodeling. Increased production of damage, or suppressed repair, could elevate the level of microdamage in bone, reducing its safety factor. Initiating an exercise program from a sedentary baseline, sudden increases in training intensity or duration could shift the normal equilibrium toward accumulation of microdamage in the skeleton. Controlled loading studies in animals demonstrate that applied loads can, indeed, increase microdamage in loaded regions and that this activates targeted remodeling [60,62,63] by a process associated with osteocyte apoptosis [64].

Conversely, suppression of normal bone turnover could reduce the rate of repair, leading to damage accumulation. In the ninth rib of beagles, bisphosphonate treatment for 12 months suppressed intracortical remodeling by 53% (risedronate) and 68% (alendronate), and this was associated with increased microdamage accumulation of 2.7 times and 4.5 times that observed in controls animals, respectively [65]. The doses used were about 5 times that used in clinical treatment, and were selected, specifically, to suppress bone remodeling without affecting mineralization. In alendronate-treated animals, the increased microdamage burden was associated with a significant reduction of 20% in bone toughness, a measure of the bone material's energy absorption capacity.

Like the rat femora in Turner and Dunipace's [13] fluoride study, the bones increased their geometric dimensions in response to the treatment, so that no reductions in breaking load or stiffness were observed. In the case of bisphosphonates, this is consistent with the clinical data demonstrating reductions in the fracture risk following 3–4 years of treatment with alendronate in women with osteoporosis [66,67]. Nevertheless, it will be important to determine the result of microdamage accumulation related to suppressed remodeling at clinical doses and over a longer period of time than 1 year for dogs, or 5–10 years in the human skeleton. These observations highlight the complex interaction between mechanical and metabolic influences on the skeleton, and the impact that pharmaceutical intervention may have on that balance.

Summary

Mechanical influences on the skeleton have important clinical relevance because of their ability to influence growth, modeling and remodeling activities that can maximize, or maintain, the determinants of fracture resistance and minimize the risk of injury. Applied mechanical loads can effect adaptations in cortical and cancellous bone, reduce the rate of bone turnover, and activate new bone formation on cortical and trabecular surfaces. In doing so, they increase the fracture threshold of bones by beneficial adaptations in the geometric

dimensions. There is no direct evidence to demonstrate anti-fracture efficacy for increased mechanical loading, but the geometric alterations engendered undoubtedly increase the structural properties of bone as an organ, increasing the resistance to fracture.

So why is exercise and physical activity in adults not as effective as loading studies suggest it should be? First of all, exercise is not synonymous with mechanical loading. Increased physical effort, or physiologic intensity, does not guarantee transfer of greater mechanical loads to the skeleton. It is difficult to 'deliver' osteogenic mechanical loads to the skeleton in ways that are convenient, acceptable and comfortable. Moreover, the intensity of exercise required to elicit skeletal adaptation in adults is relatively high, and a weekly exercise routine must be maintained in the long term to conserve bone mass. It follows that the convenience of pharmaceutical treatment is considerably more agreeable than a long-term commitment to strenuous physical activity. That is, exercise compliance may be even more difficult to achieve than medical compliance. Finally, there is the risk that loads applied to the skeleton through some physical activities may be detrimental to the joints, leading to osteoarthritis; may stimulate fatigue damage leading to stress fractures; or may interact with some treatments to increase the rate of microdamage within cortical or trabecular bone. If controlled loading of human bone is unlikely as an intervention, knowledge of the mechanotransduction pathways involved in skeletal adaptation is still essential for developing novel approaches to the induction and augmentation of osteogenesis in skeletal diseases associated with aging or disability.

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