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Low-level mechanical signals and their potential as a non-pharmacological intervention for osteoporosis

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Abstract

Background: exercise is recognised as a critical regulatory signal to the skeletal system, but which specific aspects of exercise are responsible for influencing bone mass and morphology and resisting fractures remains unknown. Recent data indicate that extremely low-level mechanical signals are anabolic to bone, and thus may be used, non-invasively, as a form of 'passive' exercise to positively influence skeletal status.
Objective: to summarise recent experimental studies on the effect of low-level mechanical signals (hypothesised to serve as a surrogate for the spectral content of muscle contractility) as a potential non-pharmacological intervention for osteoporosis.
Results: low magnitude mechanical signals are anabolic to bone if applied at a high frequency (15–90 Hz). Long-term animal studies (1 year) show that these low-magnitude mechanical signals can increase cancellous bone volume fraction, trabecular thickness, trabecular number and enhance bone stiffness and strength. Studies in the mouse have shown that these low-level signals will stimulate bone formation rate and labelled surface in cortical and cancellous bone, but the molecular and genetic regulation of this mechanosensitivity is extremely complex. Preliminary studies in children with disabling conditions and post-menopausal women indicate that such signals can be efficacious in reversing and/or preventing bone loss.
Conclusions: considering that the strains (deformations) that result from these low-level vibrations are far below (<1/1000th) those which may cause damage to the bone, we believe they represent a unique, non-pharmacological prophylaxis for osteoporosis. Given that so many physiologic systems are tuned to specific frequencies, such as sight, hearing and touch, it should not be entirely surprising that the musculoskeletal system would be responsive to frequency as well.

Keywords: *osteoporosis, mechanical, treatment, anabolic, bone, skeletal*

Background

Osteoporosis, a disease characterised by the progressive loss of bone tissue, is one of the most common complications of ageing [1]. This disease affects over 50% of women in the United States over the age of 65, requiring over $18 billion per year to treat, and annual costs are projected to exceed $250 billion within the next 50 years [2]. To date, prevention of bone loss has been approached principally through pharmacological interventions, the long-term safety of which remains uncertain [3], and which work by disrupting normal processes of bone remodelling rather than restoring them. Further, such anti-resorptive and anabolic approaches inherently ignore the fact that a significant portion of the skeleton's structural success can be attributed to bone's sensitivity to its mechanical environment, and as such, its 'form follow function' capacity could be leveraged to ensure that sufficient mass is placed to withstand the rigors of functional activity [4].

By improving our understanding of how mechanical factors can regulate bone mass and morphology, mechanical signals themselves may represent the very essence of a safe, non-invasive, non-pharmacological means to inhibit osteoporosis. In the work described here, we have found that extremely low-level mechanical signals are strongly anabolic to bone and are capable, in both animal and clinical models, of enhancing both bone quantity and quality.

Enhancing bone quantity and quality with low-level mechanical signals

The adaptive response in bone is sensitive only to dynamic (time-varying) strains; static strains are ignored as a relevant source of osteogenic stimuli [5]. This implies that a time-varying component is either directly (e.g. piezoelectric) or indirectly (e.g. fluid flow) responsible for influencing cell activity, and that magnitude of the stimulus may not be the dominant determinant of response. Further, the osteogenic potential of mechanical signals is defined by a strong interdependence between cycle number, strain magnitude and frequency. In cortical bone, 2000 microstrain (0.2% strain)

induced at 0.5 Hz (one cycle every 2 s) maintains bone mass and achieves this with just four cycles of loading encompassing 8 s per day [6]. Such magnitudes are similar to the peak strains that are generated during vigorous activity in a variety of animals [7].

Providing the first evidence of the interrelationship of load magnitude, cycle number and strain frequency, reducing the magnitude to 1000 microstrain (με) at 1 Hz in turn increases the number of loading events required to maintain bone mass to 100 cycles [8]. Raising the loading frequency to 3 Hz, bone mass can be retained with 1800 cycles (600 s of load) with peak-induced strains of only 800 με [9]. With the same 600 s per day loading regimen, only 200 με is necessary to maintain cortical bone mass if the strain is applied at 30 Hz, a protocol employing 18,000 cycles of loading. When these 30 Hz mechanical signals are induced for 1 h per day (108,000 cycles), only 70 με is necessary to inhibit bone loss. A synthesis of these data demonstrates that the sensitivity of bone to mechanical loading goes up quickly with frequency, and thus much lower strains are necessary to maintain bone mass. It is predicted that the strain magnitudes required for maintaining bone mass are even much lower than 70 microstrain if the loading frequency is increased. Thus, extremely low-level magnitudes, far below those which might cause damage to bone, can be used to augment the skeleton if delivered at a suitably high frequency.

The challenge becomes identifying a means to get these signals to the skeleton non-invasively, something that can be achieved through foot-based whole body vibration [10], which can efficiently transmit vibration through to the axial skeleton, at least through 50 Hz [11]. To determine whether long-term (12 months) signals could improve the structural status of the bone, 18 adult female sheep, 5–7 years of age, were randomised into two groups—experimental and untreated controls; for 20 min/day, 5 day/week, the experimental sheep stood constrained in a chute such that only the hind limbs were subject to a vertical ground-based vibration, delivered through a gently oscillating plate, vibrating at 30 Hz, to create peak–peak accelerations of 0.3 g [12]. These accelerations generated peak strains on the diaphyseal shaft of the tibia of less than 10 microstrain, or ×300 less than the peak strains generated during intense activity.

Using quantitative computer tomography (QCT) to selectively evaluate cortical and cancellous bone at the lesser trochanter of the femur, a 34.2% increase in trabecular density was observed in mechanically stimulated sheep (Figure 1; $P<0.01$). Bone histomorphometry demonstrated substantial increases in trabecular bone volume and trabecular number and sharp decreases in trabecular spacing [13]. Micro-computed tomography was used to model morphologic parameters of 1-cm cubes of trabecular bone harvested from the medial condyle of the femur [14]. Trabecular Bone Pattern factor, an index of connectivity, decreased 24.2% in the animals subject to the non-invasive stimulus ($P<0.03$), demonstrating an increase in connectivity and thus an improvement in the quality of bone.

To examine whether these low-level mechanical signals influenced the structural properties of the trabeculae, we performed mechanical testing on the bone cubes [14]. Stiffness in the longitudinal direction, at 410 MPa in the control animals, was 12.3% greater in the experimental animals (461 MPa; $P<0.04$). In the M–L direction, there was a 6.1% increase, but it was not significant ($P = 0.22$), neither was a 2% drop in stiffness in the A–P direction ($P = 0.39$). Strength to failure, measured only in the longitudinal direction, was 26.7% greater in the experimental animals ($P<0.05$). Computational modelling of the cancellous remodelling indicated that the adaptations were sufficient to reduce the apparent strain within each trabecular strut [15].

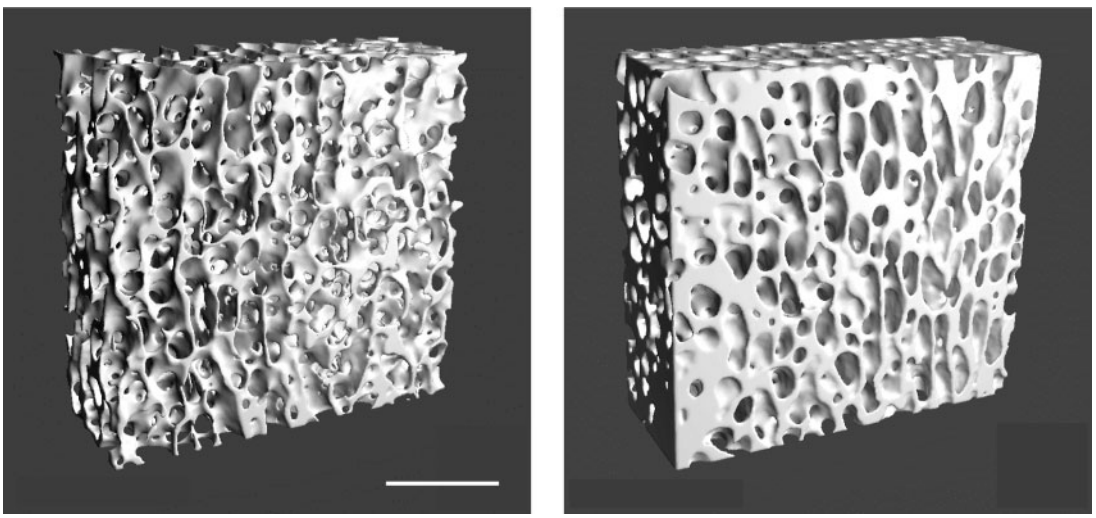

Figure 1. Three-dimensional reconstructions of trabecular bone from the distal femur in control sheep (left) as compared with the same region of experimental sheep (right), which had been subjected to 20 min per day of a low-level (0.3 g), high-frequency (30 Hz) mechanical signal. The experimental bones have improved connectivity, enhanced bone volume fraction, and are stiffer and stronger than the control bone. Scale bar is 2 mm. Adapted from Rubin *et al.* [14].

Disuse osteoporosis halted by low-level mechanical signals

The long-term protocols on sheep indicate the anabolic nature of the low-level mechanical signal. To determine whether these signals also held anti-resorptive potential, the tail-suspension model of disuse osteopaenia was used with adult, female Sprague–Dawley rats to examine whether the resorptive remodelling, as stimulated by disuse, could be suppressed with brief exposure to the oscillating plate [16]. A single-element strain gage, attached longitudinally to the tibial diaphysis of rats, used for calibration showed that, similar to the sheep studies described above, the mechanical intervention, at 0.3 g, generated strains <5 με at 45 Hz, fully three orders of magnitude below peak strains generated during vigorous physical activity [17].

Following 28 days of tail suspension, as compared with long-term controls, the tibiae from tail-suspended animals caused bone formation rate per bone volume (BFR/BV) to drop by 92% ($P<0.05$). The suppression of formation was not significantly different from the animals subject to disuse for most of the day (23 h, 50 m) and then allowed to freely bear weight for 10 min per day (–61%, $P<0.05$). However, 10 min/day of weight bearing on an active vibration platform normalised BFRs to normal weight-bearing levels at vibration frequencies of both 45 Hz (–6%, $P>0.05$) and 90 Hz (–7%, $P>0.05$).

Transducing a low-level mechanical signal into an anabolic response

As the anabolic and anti-resorptive potential of low-level mechanical signals becomes apparent, it is important to consider the physiologic relevance of these extremely small deformations. In addition to the large strains typically associated with intense activity [7], smaller magnitude strain signals are evident in bone, to a large extent arising from the spectral content of muscle contractility [18]. These small strains persist over long durations, including passive actions such as standing, and therefore represent a dominant component of the bone's functional strain history.

Similar to disuse, the ageing process invariably involves muscle wasting, or sarcopaenia [19], and we have hypothesised that the reduction in muscle activity, particularly in regard to the spectral content of muscle contractility, removes a key regulatory signal to bone and thus contributes to bone erosion [20]. Thus, even though the applied vibration signal is low relative to peak strain events, when compared with the signals normally experienced at this frequency, they are quite large. Considering how such a small signal could be transduced to a biologic response, the high dependence of fluid flow on frequency would indicate that these signals could have a disproportionate influence on perfusion of tissues, enhancing movement of nutrients and promoting streaming currents [21]. Even when the physical signal reaches a cell, its influence on transcriptional activity is extremely complex, down-regulating genes involved in bone resorption and up-regulating genes involved in bone formation, but in a manner that emphasises a sophisticated temporal and spatial control of the proteins [22].

It is important to point out, however, that other factors contribute to bone's sensitivity to mechanical signals. For example, recent evidence in mice shows that some inbred mouse strains are more responsive to mechanical intervention than others [23], not only emphasising the role of the genome in defining bone plasticity, but perhaps explaining why some human populations are at greater risk of osteoporosis, and why exercise is more effective in some groups than others.

Can low-level mechanical signals be effective in the clinic?

Mechanical signals in the form of vibration, if kept at extremely low levels (well below 0.5 g), are simple and safe to impose into the skeletal system. Considering the inherent complications of drug-based interventions to curb osteoporosis, there is clearly some potential to develop a non-pharmacological approach to the prevention of bone loss. In a prospective, randomised, placebo-controlled study, 70 women, 3–8 years past the menopause, were randomly assigned to either an experimental or a placebo group [24]. After 12 months, using linear regression of the means on bone mineral density (BMD) in the placebo group, normalised to body weight, showed a 3.3% loss (±0.83%) in the lumbar spine along with a 2.9% (±1.2%) loss of BMD in the trochanter region of the femur. In the experimental group, loss of BMD in the spine was inhibited to –0.8% (±0.82%), a 2.5% benefit of treatment ($P<0.04$). In the trochanter of the experimental group, a gain of 0.4% (±1.2%) was measured over the course of the year, a 3.5% benefit of treatment ($P<0.02$). No differences were measured at the radius between the placebo and the experimental groups. Focusing on the lighter weight (<65 kg) women, as a known risk factor for osteoporosis, and who were compliant (compliance =60%), the benefits of therapy become significant ($P = 0.03$) for the total spine with a 3% positive difference and demonstrate a net positive difference of >2% positive difference at the femoral neck and trochanter (Figure 2).

Osteoporosis is also an important problem in young children with conditions such as cerebral palsy, a condition certainly exacerbated by diminished locomotor function.

To examine the ability of low-level mechanical signals to provide a surrogate for the diminished muscular activity and thus restore bone loss in such children, a heterogeneous group of 20 pre- and post-pubertal ambulant children with disabling conditions [14 males, 6 females; mean (SD) age 9.1 (4.3), range 4–19 years] was randomised to standing on active ($n = 10$; 0.3 g at 90 Hz) or placebo ($n = 10$) devices for 10 min per day, 5 days per week, for 6 months [25]. Pre- and post-trial proximal tibial and spinal (L2) volumetric trabecular bone mineral density (vTBMD; in units of mg/ml) was measured by three-dimensional QCT.

Over the 6-month trial, the mean change in tibial vTBMD in children who stood on active devices was 6.27 mg/ml (+6.3%) whilst in children who stood on placebo devices vTBMD decreased by –9.45 mg/ml (–11.9%; Figure 3). Thus

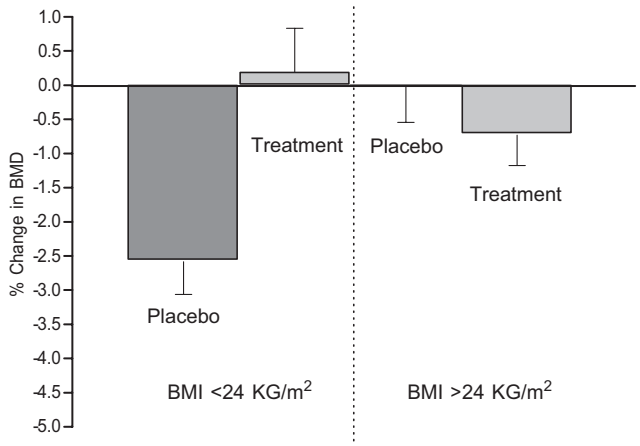

Figure 2. Lighter women (BMI<24) in the placebo group lost on the order of 2.5% bone from the spine over the course of the year. Those thinner women, when exposed to low-level mechanical stimulation, inhibited this loss (P = 0.005). As importantly, women with a BMI<24 lost no bone over the course of the year, and thus it was not possible to demonstrate the efficacy of treatment to inhibit a loss that was not occurring (P = 0.36). Adapted from Rubin *et al.* [24].

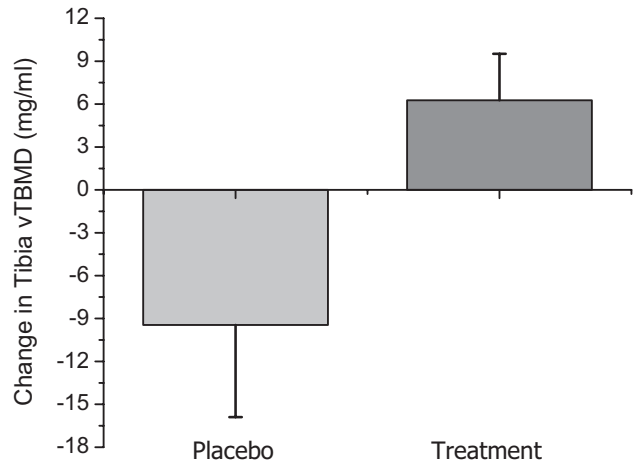

Figure 3. Over a 6-month period, volumetric trabecular bone mineral density (vTBMD) of the tibia of children with disabling conditions dropped 9% in the placebo group. In contrast, treatment with the low-level mechanical signals increased vTBMD in the tibia of the experimental group by ~6%. This 17% difference between groups was significant at P = 0.0036. Adapted from Ward *et al.* [25].

the net benefit of treatment was +15.72 mg/ml (17.7%) (95% CI = 6.57, 24.87; P = 0.0033). At the spinal site, the net benefit of treatment, as compared with placebo, was +6.72 mg/ml, (95% CI = –2.60, 16.05; P = 0.14). Compliance was 44% of the 10 min per day period (4.4 min per day), thus implying that the anabolic response could be achieved with very short duration stimuli—a phenomenon also observed in animal experiments [6].

This randomised, double blind, placebo-controlled trial indicates that low-level mechanical signals are anabolic to trabecular bone in humans, perhaps by providing a surrogate for suppressed muscular activity in the disabled. The treatment could potentially offer a non-invasive, non-pharmacological and safe approach to improving trabecular vBMD in the limbs of children with disabling conditions.

Summary

As with any intervention, the use of low-level mechanical signals must be approached with caution. More specifically, vibration is most-often associated with the musculoskeletal system as a pathogen [26], primarily in the cause of low back pain. Such concern surrounds vibration that there are international safety standards that define thresholds for human tolerance [27]. At 30 Hz, 0.3 g, such standards indicate that standing humans can safely be exposed for up to 4 h per day. However, when vibration exceeds 1.0 g, duration drops dramatically, and when levels which exceed even 10 g are considered for the treatment of the elderly [28], not only the potential chronic damage [29] but also the acute damage should be considered [30]. As with any potential therapy, it is essential to consider whether the benefits outweigh the consequences.

Mechanical signals are considered critical to the skeleton, a perspective that is best recognised through the clear benefit of exercise on achieving and retaining bone health. Animal and clinical work presented here indicate that, in addition to large loads that might arise through vigorous activities, extremely low-level mechanical signals are omnipresent in the skeleton's loading history and are anabolic to bone tissue. Considering that these signals are orders of magnitude below those that generate damage to bone, it is possible that they hold great potential for the non-pharmacological prevention and/or treatment of osteoporosis. While these mechanical signals are native to the bone tissue, safe at low intensities and incorporate all aspects of the remodelling cycle [31], the widespread use of mechanical stimuli in the treatment of skeletal disorders will undoubtedly be delayed until we achieve a better understanding of the mechanisms by which they act. Nevertheless, the osteogenic potential of mechanical stimuli clearly points to their potential as a unique, non-drug intervention for disorders and injuries of the musculoskeletal system.

Acknowledgements

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Key points

- Low-level, high-frequency mechanical signals are anabolic to bone tissue.

- Osteoporosis can be prevented by introduction of low-level, high frequency signals.
- These signals may represent a non-pharmacological basis for the preservation of musculoskeletal integrity.
- These stimuli may represent a surrogate to muscle-based signals which decay with ageing.

References

1. NIHConsensus Development Conference. Osteoporosis prevention, diagnosis, and therapy. NIH Consens Statement 2000; 17: 1–45.
2. Carmona R. Bone Health and Osteoporosis: A Report of the Surgeon General. US Health and Human Services, 2004.
3. Lacey JV Jr, Mink PJ, Lubin JH *et al.* Menopausal hormone replacement therapy and risk of ovarian cancer. JAMA 2002; 288: 334–41.
4. Wolff J. Das Gesetz der Transformation der Knochen (The Law of Bone Remodelling). Berlin: Verlag von August Hirschwald, 1892.
5. Lanyon LE, Rubin CT. Static vs dynamic loads as an influence on bone remodelling. J Biomech 1984; 17: 897–905.
6. Rubin CT, Lanyon LE. Regulation of bone formation by applied dynamic loads. J Bone Joint Surg [Am] 1984; 66: 397–402.
7. Rubin CT, Lanyon LE. Dynamic strain similarity in vertebrates; an alternative to allometric limb bone scaling. J Theor Biol 1984; 107: 321–7.
8. Rubin CT, Lanyon LE. Kappa Delta Award paper. Osteoregulatory nature of mechanical stimuli: function as a determinant for adaptive remodelling in bone. J Orthop Res 1987; 5: 300–10.
9. Qin YX, Rubin CT, McLeod KJ. Nonlinear dependence of loading intensity and cycle number in the maintenance of bone mass and morphology. J Orthop Res 1998; 16: 482–9.
10. Fritton JC, Rubin CT, Qin YX *et al.* Whole-body vibration in the skeleton: development of a resonance-based testing device. Ann Biomed Eng 1997; 25: 831–9.
11. Rubin C, Pope M, Chris FJ *et al.* Transmissibility of 15-hertz to 35-hertz vibrations to the human hip and lumbar spine: determining the physiologic feasibility of delivering low-level anabolic mechanical stimuli to skeletal regions at greatest risk of fracture because of osteoporosis. Spine 2003; 28: 2621–7.
12. Rubin C, Turner AS, Bain S *et al.* Anabolism: low mechanical signals strengthen long bones. Nature 2001; 412: 603–4.
13. Rubin C, Turner AS, Mallinckrodt C *et al.* Mechanical strain, induced noninvasively in the high-frequency domain, is anabolic to cancellous bone, but not cortical bone. Bone 2002; 30: 445–52.
14. Rubin C, Turner AS, Muller R *et al.* Quantity and quality of trabecular bone in the femur are enhanced by a strongly anabolic, noninvasive mechanical intervention. J Bone Miner Res 2002; 17: 349–57.
15. Judex S, Boyd S, Qin YX *et al.* Adaptations of trabecular bone to low magnitude vibrations result in more uniform stress and strain under load. Ann Biomed Eng 2003; 31: 12–20.
16. Rubin C, Xu G, Judex S. The anabolic activity of bone tissue, suppressed by disuse, is normalised by brief exposure to extremely low-magnitude mechanical stimuli. FASEB J 2001; 15: 2225–9.
17. Rubin CT, Lanyon LE. Limb mechanics as a function of speed and gait: a study of functional strains in the radius and tibia of horse and dog. J Exp Biol 1982; 101: 187–211.
18. Fritton SP, McLeod KJ, Rubin CT. Quantifying the strain history of bone: spatial uniformity and self-similarity of low-magnitude strains. J Biomech 2000; 33: 317–25.
19. Rosenberg IH. Sarcopenia: origins and clinical relevance. J Nutr 1997; 127: 990S–1S.
20. Huang RP, Rubin CT, McLeod KJ. Changes in postural muscle dynamics as a function of age. J Gerontol A Biol Sci Med Sci 1999; 54: B352–7.
21. Qin YX, Kaplan T, Saldanha A *et al.* Fluid pressure gradients, arising from oscillations in intramedullary pressure, is correlated with the formation of bone and inhibition of intracortical porosity. J Biomech 2003; 36: 1427–37.
22. Judex S, Zhong N, Squire M *et al.* Mechanical modulation of molecular signals, which regulate anabolic and catabolic activity in bone tissue. J Cell Biochem 2005; 94: 982–994.
23. Judex S, Donahue LR, Rubin CT. Genetic predisposition to osteoporosis is paralleled by an enhanced sensitivity to signals anabolic to the skeleton. FASEB J 2002; Express Article 10.1096/fj.010913fje.
24. Rubin C, Recker R, Cullen D *et al.* Prevention of postmenopausal bone loss by a low-magnitude, high-frequency mechanical stimuli: a clinical trial assessing compliance, efficacy, and safety. J Bone Miner Res 2004; 19: 343–51.
25. Ward K, Alsop C, Caulton J *et al.* Low magnitude mechanical loading is osteogenic in children with disabling conditions. J Bone Miner Res 2004; 19: 360–9.
26. Griffin MJ.Predicting the hazards of whole-body vibration – considerations of a standard. Ind Health 1998; 36: 83–91.
27. International Standards Organization. Evaluation of Human Exposure to Whole-Body Vibration. Geneva: ISO, 1985.
28. Verschueren SM, Roelants M, Delecluse C *et al.* Effect of 6-month whole body vibration training on hip density, muscle strength, and postural control in postmenopausal women: a randomised controlled pilot study. J Bone Miner Res 2004; 19: 352–9.
29. Burr DB, Forwood MR, Fyhrie DP *et al.* Bone microdamage and skeletal fragility in osteoporotic and stress fractures. J Bone Miner Res 1997; 12: 6–15.
30. Bernard B, Nelson N, Estill CF *et al.* The NIOSH review of hand-arm vibration syndrome: vigilance is crucial. National Institute of Occupational Safety and Health. J Occup Environ Med 1998; 40: 780–5.
31. Rubin J, Fan X, Biskobing DM *et al.* Osteoclastogenesis is repressed by mechanical strain in an *in vitro* model. J Orthop Res 1999; 17: 639–45.