J Musculoskelet Neuronal Interact 2017; 17(3):155-161

Journal of Musculoskeletal and Neuronal Interactions JMNI

Perspective Article

Exercise for osteoporosis: how to navigate between overeagerness and defeatism

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Abstract

Osteoporosis and associated fractures remain a common and costly health problem. Public fears about rare side effects of efficacious drug treatments for osteoporosis have contributed to decreased prescription and compliance. Exercise and physical activity-based interventions have long been proposed as an alternative treatment for osteoporosis. However despite compelling evidence from experimental studies in animals and from observational studies in humans, the use of exercise to improve bone mass in clinical practice does not seem to be justifiable by current human interventional studies. In this perspective, we summarise the available evidence in support of exercise on bone mass. We review the modest effects observed in current exercise trials, and propose a number of factors which may contribute to these discrepancies. We also highlight the successful application of exercise to attenuating or even partially reversing bone loss in musculoskeletal disuse. We then propose how collaboration between basic science and clinical partners, and consideration of factors such as exercise modality, exercise intensity and participation motivation could improve exercise efficacy.

Keywords: Bone, Mechanoadaptation, BMD, Physical Activity

Osteoporosis can be defined as "a disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk"[1]. Despite the availability of increasingly efficacious anti-resorptive and anabolic drugs, osteoporosis and related fractures continue to be a burden for our aging population. This has led to the recent launch of a 'call to action' to address the crisis in the treatment of osteoporosis by ASBMR, together with 34 other health organisations[2]. Exaggerated concerns about side effects of some drugs have led to reduced prescription and patient compliance[3], and so many cling to the old idea of using exercise in order to prevent osteoporosis. This is distinct from the role of exercise in reducing fall incidence[4,5] - falls and osteoporosis being independent risk factors for fracture[6]. However, skeptical voices are heard here as well, stating that exercise benefits for bone have been over-enthusiastically championed over the last two decades. Admittedly the current body of literature shows only small to moderate increases (from 1-8%) in bone mass as a result of exercise trials in children[7-11]. Effects in adults are also minor[12-14]; even in the most successful, long-term trials in older adults, bone mass increases are modest (around 1-3%)[15-17]. Thus, since life-long bone losses can amount to up to 40% in some bones[18], the clinical benefit of exercise for bone is currently very limited. This perspective examines current observational and interventional evidence for the effects of exercise on bone mass, and proposes how efficacy of interventions can be improved.

Mechanical stimuli are key for development and maintenance of bone health

It is quite clear that bones adapt to their mechanical environment, an idea now in its third century[19]. Bone size, mass, shape and ultimately strength are regulated according to the habitual level of strain experienced[20,21]. The importance of these mechanical stimuli for bone health is evident from the earliest to the latest stages of human life. Fetal immobility due to central nervous disorders results in slender, hypomineralised bones highly prone to fracture[22].

The authors have no conflict of interest.

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Edited by: S. Warden
Accepted 16 May 2017

Delayed motor development in early childhood leads to large, persisting deficits in bone mass[23-25], whilst childhood spinal cord injury (SCI) and subsequent reduced movement results in smaller, weaker, more circular bones[26]. Following skeletal maturity, disuse and immobility results in substantial loss of bone mass[27] e.g. 20-60% in long-term SCI dependent on site[28,29], through cortical thinning and reduction in trabecular density. The absence of an age effect on bone losses following SCI[30] suggests that mechanical stimuli remain key for maintenance of bone health into old age.

Strong observational evidence suggests a large potential of exercise for bone

Physical exercise is an obvious and natural way to modulate the bone's mechanical environment, and one would expect that increased loading via physical activity should lead to bigger, stronger bones. Thus, it has been known for decades that cortical thickness of the humerus can be one third greater in the racquet arm of tennis players as compared to the other side[31]. Moreover, leg bones of competitive runners are one fourth stronger than in inactive peers[32], and these bone benefits persist into middle and older-age[33]. Whilst these latter observations might be affected by underlying genetic or nutritional differences, the 30-40% greater bone mass observed in the active compared to inactive arm of tennis[34,35] and baseball[36] players is hard to explain by anything other than effects of exercise. However, some types of exercise are more beneficial than others; the most pronounced effects are observed in vigorous sports involving an impact element[32,37,38]. Indeed, popular activities such as swimming and cycling appear to have little benefit for lower limb bone health[32,37,39]. It is important to recognize that sports are not primarily designed to improve bone health, and hence the osteogenic stimulus provided by exercise modes deliberately targeting bone should likely be even greater than that suggested by current observational reports.

Current exercise interventions in ambulatory individuals have not realized this potential

The observed exercise 'benefits' for bone suggested by these studies has provided a rationale for exercise-based intervention studies for bone. As early as four decades ago a 12-month, tri-weekly intervention of gym-based exercise in postmenopausal women was shown to lead to small (~2.5%) but significant increases in bone mass (assessed as total body calcium)[40]. Since this initial study, dozens of randomized controlled trials have investigated the effects of different exercise interventions on bone strength in males and females of all ages. Systematic reviews and meta-analyses suggest that while moderate exercise benefits to bone are consistently observed in children, effects in adults are minor or absent[7-9,12-14]. Authors of these reviews highlighted that evidence was limited by poor quality of studies and heterogeneity of exercise type, study length, sample size and weekly training load. In per-protocol analyses, some encouraging results are found - particularly in studies employing high-impact activities in children such as jumping where site-specific increases in bone mass of up to 8% are observed. However, in adults of all ages results are unimpressive, with increases in bone mass of no more than 2.5% reported. Clearly, exercise interventions in healthy, ambulatory individuals have not replicated the impressive results observed in observational studies.

Exercise interventions are highly effective against disuse-related bone loss

In addition to studies aiming at bone accrual in ambulatory individuals, another group of studies has explored the potential to prevent disuse-related bone loss. The scope of this research has been the bone loss in elderly or paralyzed patients as well as in space sojourns[41]. Numerous bed rest studies have been performed as a ground-based model for spaceflight[42] in order to identify suitable exercise countermeasures for bone during the past two decades. Notably in this disuse model, monthly bone losses of 1-2% occur in areas such as the lower limbs and spine used to heavy loading during movement. From these studies, it has become clear that resistive exercise, ideally in combination with whole-body vibration, is able to prevent bed rest-induced bone loss entirely[43-45]. Astounding effects of exercise interventions have also been observed when patients with long-term spinal cord injury load their bones via high-intensity electrically stimulated isokinetic movements. Results show that 30% of the lost bone mass could be recovered in less than six months[46] whilst similar benefits to trabecular bone mass were still evident at the end of a longer-term trial[47]. Thus, there is little doubt that physical exercise can be particularly effective against a complete lack of physical activity. This is promising given that women and elderly individuals at highest risk of osteoporosis typically have very low levels of physical activity[48], particularly vigorous activities known to be osteogenic[49]. Whilst disuse-related bone losses in bed rest can be rapidly and fully recovered following reambulation[50], the ability to recover is dependent on resumption of regular loading. This is illustrated by recovery of patellar bone mass closely tracking improvements in maximal force during rehabilitation from an anterior cruciate ligament (ACL) injury[51]. Similarly, in ACL patients treated more conservatively (whereby non-weight bearing time is minimized), bone mass losses are minimal compared to the large losses which follow surgical treatment and subsequent immobilization[52].

Why have interventions to accrue bone been ineffective so far?

So, from the existing literature it seems that previous clinical trials have under-achieved, and that bones can be more responsive to exercise than suggested. Fundamentally, trials have rarely targeted inactive individuals - particularly in children, whereby interventions are applied on top of a high level of habitual physical activity. As exemplified by

effects of exercise in disuse conditions, it would be expected that substantial bone benefits would only be achieved when exercise represented a large departure from habitual loading levels. As objective measures of bone loading (or even surrogates such as accelerometry) are not commonly collected prior to and during exercise intervention periods, any alteration in overall loading cannot be quantified. Important clues are also offered by results of the longest continuous exercise trial for bone, whereby the minimum effective dose of exercise for hip and spine bone mass over a 16-year period was two sessions per week, and exercise volume predicted bone benefits[53]. Thus, past clinical interventions likely have failed to provide effective magnitudes of loading. Similarly, bone strength benefits in master track athletes are greater in sprint than middle-distance and in turn long-distance runners in line with the speed (and hence muscle and reaction forces of the event)[33]. Little or no bone strength benefit is evident in competitive race-walkers despite high training volumes and a long training history[33]. This is likely due to the low ground reaction (and presumably muscle) forces evident in race walking, which at ~1.5 times bodyweight (BW)[54], are similar to conventional walking (1.2 BW) and much lower than running (2.5BW)[55] or sprinting (4.5 BW)[56]. Therefore in addition to sufficient volume, interventions must ultimately be performed at a high intensity (likely meaning large forces) and targeted at inactive individuals to ensure substantial benefits.

Secondly, the timing and duration of physical activity is likely to be important. Whilst substantial bone mass benefits were evident in the racquet arms of older tennis players who had begun playing in adulthood, far greater advantages were observed in those individuals that played across their entire life-span[57]. It is reasonable to assume that experience in the particular sport contributes to this effect - old people simply do not learn a new sport as easily as young people. However, it also appears that the ability to increase bone size via exercise in adulthood is limited (particularly at epiphyseal sites)[57-59], emphasizing the importance of exercise during skeletal development. Whilst advantages in bone strength attributable to lifelong exercise appear to diminish with age[57,60] (likely due to a reduced ability to increase muscle size and strength[57]), substantial advantages are evident even at 70 years of age[57]. However, it is only the advantages in bone outer geometry which persist long-term following cessation of exercise, as benefits to bone mass diminish[36]. Therefore whilst some bone benefits from exercise persist from childhood and can be gained in later life, development and maintenance of *optimum* bone health relies on long-term adherence to exercise. Bone response to altered loading is much slower than that in muscle, with bone loss following spinal cord injury taking up to 8 years to reach a steady state[29]. Hence, bone benefits observed even after interventions lasting several months are unlikely to reflect those attainable by adherence to long-term, progressive exercise programmes.

A third point to consider is motivation. This has not been assessed in the past trials, but why would a study participant train as frequently and hard as a competing athlete? Overall, high compliance rates in exercise interventions targeting bone[61] give cause for optimism, being much higher than patient compliance for pharmacological osteoporosis treatments[62]. However, compliance for high-intensity programmes is lower than for moderate-intensity regimes, emphasizing the importance of maintaining participant motivation. Relevant aspects include non health-related benefits such as enjoyment and social interaction, and self-efficacy - the patient's belief in their ability to perform a given exercise. Whilst injury rates may not be increasing with age[63], it is certainly more difficult for an older person to practice novel exercise modes than for a younger person.

Fourth, and as emphasized previously, the mode of exercise is critical and interventions have typically not mirrored those exercises (running and bounding, hitting or throwing activities, etc.) associated with greatest bone strength in athlete studies. Where interventions have employed sports associated with good bone health, results have been quite impressive even in older individuals[64,65]; although the lack of trials comparing these exercises to traditional approaches is a limitation.

Recent advances in measurement techniques have allowed first measurement of the complex deformation patterns experienced by bone during exercise, such that understanding of factors contributing to a particular movement's osteogenic potency can be identified. This new information can complement - and even drive - existing computational modelling approaches used to estimate site-specific loading[66] and adaptation[67] to different exercise movements. In addition to substantial compressive and bending loads expected, it is now clear that large torsional stresses (attributable to muscular action[68]) act on the lower limbs during walking and running[69]. Whilst the mode of deformation (compressive, bending or torsion) has previously received little attention, torsional stresses appear to be key to the development of long bones[70]. These torsional stresses are most evident during a forefoot running action used by sprinters, and in upper limb movements such as throwing and tennis service strokes[71]. Therefore it is unsurprising that these movements are those associated with the greatest bone benefits observed in athletes.

What must be done?

We are understanding biomechanics and the physiology of bone adaptation more deeply now than a decade ago. It emerges in particular that muscular contractions are more important than collision with external objects[72], in their role provoking or helping the body to negotiate these collisions . Moreover, in addition to strain magnitude and strain rate, the deformation mode (in particular torsional loading) also has to be considered as relevant.

The lessons learnt now need to be taken on board, in collaboration between the various clinical partners. The experience of geriatricians and allied health professionals e.g. physiotherapists is key in utilising basic science knowledge to develop individualized interventions based on a patients'

capabilities and motivation. These tailored interventions should be oriented towards movements such as running, batting and throwing that are associated with large bone benefits in athletes, where volume and intensity of exercise can be easily monitored and progressively increased, and which importantly are not dependent on the acquisition of highly technical and unfamiliar movement skills. Particular attention should be given to the motivation of participants, through e.g. introduction of competitive and social elements to exercise.

Whilst exercise could be considered as a natural alternative to pharmacological interventions, it is also important to explore the extent to which it complements these proven treatments. At present only a few studies have investigated interactions between exercise and anti-resorptives, although early results are promising[73,74]. Bisphosphonates had an additive effect in reducing bone loss in astronauts when combined with resistive exercise[75], and similar effects were observed in lung transplant patients such that patients on combined therapy saw substantial gains (~10%) in lumbar spine bone mass[76]. However, the first and largest RCT of bisphosphonates and exercise found separate but no additive effects of the two treatments[77].

A multi-centre study along the lines proposed above and designed by multiple stakeholders is the only way to establish rigorous evidence for the broader application of these interventions. In addition, development of an effective human exercise model will allow exploration of other factors relevant to interventional design, which may influence the mechanoadaptive response and thereby intervention efficacy. For example, animal studies have shown that bone mass gains in response to exercise are also highly dependent on the number[78,79] and timing[80,81] of exercise repetitions and training sessions but these factors remain largely unexplored in humans. Similarly, changes in bone mass attributable to different exercise modes result in highly direction-specific changes in mechanical strength[67]. Such information is not available from clinical dual-energy X-ray absorptiometry (DXA) scans commonly employed in exercise trials, which unlike volumetric methods such as quantitative computed tomography (QCT) may underestimate effects of mechanical loading on bone[82]. Consideration of fracture mechanics in regions such as the proximal femur could further improve the efficacy of bone mass gains in reducing fracture risk[83]. Once the viability of exercise as an alternative or complementary treatment for osteoporosis is established in the same way as for weight loss and cardiovascular health, acceptance of more effective, unconventional movement types will be easier to achieve.

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