Title: Exercise in the prevention of osteoporosis-related fractures

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Running Head: Exercise and bone

Keywords: EXERCISE, OSTEOPOROSIS, BONE MASS, HIP FRACTURE, BONE STRENGTH, PHYSICAL ACTIVITY

SUMMARY

The prevention of osteoporotic fracture by exercise intervention requires a two-pronged approach; that is, the maximization of bone strength and the minimization of falls. The former is most effectively addressed before peak bone mass has been attained, so that the latter is the primary option for the older, osteoporotic individual. Intense animal and human research activity over the last twenty years has generated a wealth of data that has led to recommendations for exercise prescription to both enhance bone strength, and minimize risk of falling. Whether those exercise protocols will be shown to effectively reduce actual fracture incidence requires the analysis of longer term data than is currently available.

1. INTRODUCTION

The utility of exercise in preventing osteoporosis-related fractures is a topic of considerable interest and research effort. It is well-known that skeletal unloading, such as occurs following spinal cord injury, prolonged bed rest, limb immobilization, and microgravity, precipitates generalized skeletal loss, particularly in bones that bear weight under normal conditions[1-6] and that losses may not be entirely regained with return to normal weight bearing[7]. By contrast, the effect of additional loading (exercise) on the skeleton is both variable and only modestly understood. The bone response to exercise varies as a function of skeletal age, diet, reproductive hormone status and nature of the activity.

In humans, the practical goal of an exercise intervention is not merely to increase bone mass, but to reduce the incidence of fracture. The etiology of osteoporotic fractures includes both low bone mass and falls. Falls account for over 90% of hip fractures and over 50% of vertebral fractures. Thus, developing exercise interventions that serve to improve bone mass *and* prevent falls is necessary to reduce the risk of fracture.

This chapter provides a discussion of exercise as a strategy to reduce the factor of risk (a predictor of fracture risk), in order to maximize skeletal health and prevent osteoporosis-related fractures. We summarize the literature specific to promoting bone health across the lifespan with critical reference to study design. Guidelines for prescribing exercise to reduce the factor of risk are proposed and directions for future research are identified.

2. FACTOR OF RISK

The factor of risk, based on engineering principles, is defined as the ratio between the applied load and the fracture load (ϕ = applied load/fracture load). If the applied load is greater than the fracture load, then fracture is probable. If the applied load is less than the fracture load,

fracture is unlikely. In a 70-year old individual with average hip bone mass, the factor of risk of hip fracture ranges from 1.25 to 3.0 for a fall from standing height[8-10].

Exercise is a potentially powerful strategy to reduce the risk of hip fracture by altering both the numerator and denominator of the factor of risk. It can affect the numerator in two ways. First, by eliminating falls, the numerator becomes zero and fracture becomes highly unlikely. Second, by improving lower extremity neuromuscular function, exercise can reduce applied load at the hip by lowering the energy of a fall to the side. To raise the denominator, exercise can increase bone mass and reduce skeletal fragility, thus increasing the force required to fracture.

Given the strong relationship between a bone mass surrogate (DXA-derived bone mineral density - BMD) and failure load, increasing BMD is an important strategy for reducing fractures[11-13]. Bone strength is also strongly influenced by its geometric proportions. Small increases in cross-sectional area, width and moment of inertia, convey disproportionately large improvements in the resistance of long bones to bending[14]. Effecting changes in cross sectional geometry is therefore an important strategy to reducing the factor of risk. Recent advances in the non-invasive measurement of bone geometry have improved measurement validity and reliability of techniques such as QCT[15], pQCT[16-22], quantitative ultrasound[23] and MRI[24], with commensurate improvement in our understanding of exercise effects.

3. EXERCISE STUDY DESIGN

The influence of study design and implementation on the ability to interpret research findings is particularly relevant when examining the effect of exercise on bone. In general, cross-sectional data reveals that physically active individuals have superior bone mass than those who are less active. An important limitation of cross-sectional data, however, is that of self-selection bias. That is, individuals who select a specific type of exercise may have predisposing skeletal

attributes that influence the initial choice to participate and the ability to successfully continue the activity, without injury. For example, while power lifters have higher than average bone mass, the ability to succeed in a sport that entails repetitive lifting of very heavy weights depends on an inherently strong skeleton from the outset. This predisposition will largely account for the larger bones observed in power lifters in comparison with non-weight lifting individuals. Another limitation of most cross-sectional exercise studies is the use of standard physical activity questionnaires (PAQs). Most PAQs are designed to measure energy expenditure and do not assess the magnitude of forces applied to the skeleton during an activity. Attempts to relate bone mass to total energy expenditure introduce validity error and, as a consequence, the likelihood of drawing inappropriate conclusions. As in most forms of clinical research, randomized, controlled, intervention trials (RCTs) are the most valid method to examining the effects of exercise on bone.

In the following chapter, we have chosen to emphasize observations derived from exercise RCTs with bone as the primary outcome measure. Cross-sectional observations are included where appropriate to illustrate consistency in experimental findings or when RCT data is absent or equivocal.

4. GENERAL PRINCIPLES OF EFFECTIVE BONE LOADING

4.1 Principles of exercise training

Drinkwater[25] emphasized the need to incorporate the following five principles of exercise training into the design of exercise interventions for bone health: specificity, overload, reversibility, initial values, and diminishing returns. While the principles are clearly interrelated, independent consideration will assist in the development of customized programs of training for bone.

4.1.1. Specificity

According to the principle of specificity, an exercise protocol should be designed to load a target bone. For example, lower body resistance and impact exercise will improve bone mass at the hip, but not the spine. Only when upper body resistance exercise is added will spine bone mass increase[26]. Similarly, lower extremity impact activities that prevent bone loss at the hip, do not influence bone mass at the forearm[27].

4.1.2. Overload

Exercise must overload bone in order to stimulate it. That is, loads experienced at the skeleton must either be sufficiently different from, or greater in intensity than normal daily loading to stimulate adaptive accretion[28]. Lack of attention to overload is a frequent shortcoming of published intervention studies, and one that is particularly challenging to address given the difficulty of directly measuring loads experienced at skeletal sites during exercise. Existing techniques are highly invasive and impractical for many sites.

Although not definitive, it is possible to make inferences from studies examining high versus low intensity loading to illustrate the principle of overload. For example, high intensity strength training (>80% of one repetition maximum) more effectively increases spine and hip bone mass than low or moderate intensity strength training[29, 30]. Similarly, weight squatted over the course of a 1-year progressive strength training program positively predicted change in trochanteric BMD[31]. Recently, the relationship between exercise intensity measured by accelerometry and hip bone mass was reported for a cohort of premenopausal women over the course of a year[32]. It was found that physical activities that induced accelerations exceeding 3.6g were positively related to bone mass at the hip, suggesting an exercise intensity threshold may exist. Advances

in technology that will improve our ability to directly measure bone strain during exercise will facilitate quantification of the overload principle.

4.1.3. Reversibility

When exercise is an adaptive stimulus, reversibility is demonstrable. That is, cessation of an activity reverses exercise-induced bone accretion. It is possible that the principle of reversibility applies only to mature adult bone[33-35], rather than to the growing skeleton. Recent data indicates that gains achieved from increased mechanical loading during growth are maintained in the medium long term[36], but longer term data are yet to be reported. Cross-sectional adult data are supportive of a bone maintenance effect from childhood loading, as individuals who exercised before or during puberty have significantly higher bone mass in adulthood than those who were less active[37]. These data are, however, subject to the previously mentioned self-selection bias.

4.1.4. Initial values

The principle of initial values refers to the concept that responses from bone are greatest in individuals with lower than average bone mass. For example, premenopausal women with the lowest initial bone mass demonstrated the greatest improvement at the hip to12 months of impact plus resistance training[26]. Interventions targeting postmenopausal cohorts with low bone mass have observed exercise-induced gains in spine and/or hip bone mass that are over twice as high[38, 39] as reported gains in similar cohorts with average bone mass[29, 30, 33, 40-42].

The initial values effect is likely to reflect the principle of overload, as smaller lighter bones will experience greater strain than larger heavier ones exposed to the same load. When loading is extremely high (>10 body weights), skeletal improvements are observed regardless of initial

values[43], suggesting that even very robust skeletons will be overloaded at such high load intensities.

4.1.5. Diminishing returns

The principle of diminishing returns is evident when a ceiling effect in bone adaptation is observed after a period of same or like loading. Diminishing returns is similarly related to the principles of initial values and overload, as bone will be strained less by the same load once mass and geometric adaptations to an exercise stimulus have taken place. Indeed, it is the *raison d'être* of the adaptive response to mechanical loading.

4.2. Characteristics of bone response to exercise loading

Important factors that distinguish the exercise response of the skeletal system from other body systems are: 1. changes are typically small (1-5%), 2. the time required to elicit a measurable response is considerable, 3. overload is required from the outset, 4. older bone is less responsive than younger bone, and 5. exercise-induced improvements in bone strength can occur in the absence of BMD change via geometric adaptation.

Whereas both the neuromuscular and cardiovascular systems typically respond to a training stimulus within four to six weeks, bone requires at least six months to initiate measurable adaptation, that is, complete a full remodeling cycle, and achieve a modicum of mineralization in new osteoid.

In contrast with the soft tissue systems that require progressive loading increments to prevent injury, it is increasingly clear that bone does not require a such a graduated approach[44, 45]. In fact, as described above, substantial overload is critical to stimulate a response from bone. Depending upon the age and health status of the individual, however, progressive incremental loading may be necessary to allow neuromuscular adaptation and prevent non-bone injury.

Although there is some data to the contrary[46], it is thought that bone age will influence the skeletal response to exercise[47]. Not only does younger human bone appear to respond more vigorously to a similar activity than older bone[45], but a younger individual can withstand higher load magnitudes than an older person. Thus, it is likely that exercise prescription to strengthen bone or reduce bone loss in the elderly requires some creativity.

Substantial gains in the resistance of a long bone to bending and fracture can be achieved by the strategic addition of even small amounts of new bone around the circumference of the shaft[48]. While changes in bone mass are not always observed following exercise intervention, measurement of the cross-sectional geometry of a long bone before and after an intervention may reveal these subtle but critical structural improvements.

4.3. Important load parameters

Animal data has clearly shown that bone responds preferentially to certain forms of mechanical loading. It has long been known that, when other factors remain constant, high magnitude loads that induce relatively large bone strains (deformations) are more osteogenic than low[49]. As the frequency (cycles per second) of loading increases, however, the magnitude of the load required to stimulate an adaptive response from bone declines[50]. Strain rate (the speed at which a bone deforms under load), is also a highly influential adaptive stimulus[51]. And finally, strain gradient, or the pattern of strain experienced across a loaded bone, is known to direct the location of bone remodeling[52].

5. EXERCISE STUDIES ACROSS THE LIFESPAN

5.1. Exercise and peak bone mass

The NIH Consensus Conference on Osteoporosis[53] reported that optimizing peak bone mass should be a primary strategy to prevent osteoporosis.

5.1.1. Children, exercise and bone - Cross-sectional observations

Studies of children and adolescents of various races/ethnicities generally support significant associations between physical activity and total body, hip, spine and forearm bone mass[54-62]. Evidence is accumulating to suggest that exercise confers the greatest long-term benefit when initiated in the prepubertal years[37, 63], however, the data is not consistent.

Prepubertal gymnasts have greater bone mass at weight bearing sites than controls, an effect that strengthens as years of training increases[57, 58, 64]. Compared with less active children, highly active children have a greater rate of bone mineral accumulation for the two peripubertal years during which bone is most rapidly accruing (12.5 years for girls and 14.1 years for boys)[62]. Bailey and colleagues noted that this greater accrual translated into 9% and 17% higher total body bone mineral content one year after peak bone mineral content velocity for active boys and girls, respectively. Slemenda and associates[65], however, found no relationship between physical activity and bone mass in peripubertal children. They suggested that exercise exerts an influence on bone mass before puberty, but that during puberty other factors, such as estrogen, become more influential on bone acquisition. By contrast Haapasalo and others[66] reported that the differences in spine bone mass of athletic and control children were greatest at the peripubertal years Tanner stages IV and V (average ages 13.5 and 15.5, respectively). The lack of consistency in reports likely reflects the inability of cross-sectional study design to control for the myriad of variables that influence skeletal status in growing children.

Variations in skeletal response to different activities reflect the different loading patterns of each sport and exemplify the principle of specificity[61, 67]. The effect is elegantly demonstrated by a comparison between limbs. Dominant limbs have greater bone mass than non-dominant limbs[68], and athletes loading their dominant limbs preferentially while exercising develop even

greater bilateral disparity[69, 70]. Differences in bone mass between playing and non-playing arms in female squash and tennis players are about two times greater if participation in the sport begins prior to or during menarche than after puberty[37], although some have observed that the effect does not become evident until the adolescent growth spurt or Tanner Stage III (mean age 12.6 years)[66].

In general then, the data from the majority of cross-sectional studies would suggest that exercise benefits to the skeleton are site-specific and best achieved when exercise is performed before puberty and/or during the peripubertal years.

5.1.2 Pediatric exercise intervention findings

The influence of exercise intervention on growing bone has become a focus of intense research interest in recent years.

5.1.2.1. Infants

In a study of premature infants, five repetitions of range of motion, gentle compression, flexion and extension exercises five times a week induced greater acquisition of bone mass at four weeks in exercised babies than in controls[71]. A similar protocol initiated at one week of age prevented typical postnatal loss of tibial speed of sound (a marker of bone strength) in very low birth weight infants[72]. Others have observed, however, that calcium intake exerts a greater influence on bone mineral accrual than 18 months of either gross or fine motor activity in six-month-old infants[73].

5.1.2.2. Preschoolers

The only intervention to target bone health in preschoolers assessed the material and structural response of bone of children randomized to gross motor activities compared with fine motor activities 30 min/day, 5 d/wk for 12 months[74]. Within each group children were also

supplemented with calcium (1000 mg/d) or placebo. Exercise alone increased tibial periosteal and endosteal circumferences, but exercise plus calcium improved leg bone mass, cortical thickness and cortical area of the distal tibia most markedly (Figure 1). While the differences in periosteal circumference remained between the groups twelve months after cessation of the intervention, the investigators reported that persistently higher activity levels among those in the gross motor activity group may have accounted for the disparity[75].

5.1.2.3. Pre-puberty

In a randomized study of 89 prepubescent boys and girls (mean age = 7.1 years), jumping 100 times, 3 d/wk at ground reaction forces of eight times body weight, increased femoral neck and lumbar spine bone mass 4.5% and 3.1%, respectively, in comparison with controls[76]. The effect was maintained seven months after detraining[36] suggesting the program may have augmented peak bone mass (Figure 2). Geometric changes have also been observed in response to exercise training in this age group. Femoral mid-shaft cortical thickness increased in prepubertal boys after eight months of weight bearing activity[77]. Similarly, two years participation in a school-based, high-impact, weight bearing exercise program that supplemented regular physical education enhanced structural properties of the femoral neck in prepubescent boys (mean age 10.2 years) compared to controls[78]. A mere ten minutes of jumping activity twice-weekly for nine months improved both femoral neck geometry and spine bone mass compared with controls in a healthy cohort of peripubertal boys and girls (mean age = 13.7 yrs) (Weeks and Beck, unpublished data).

Favorable responses to bone loading exercise that included resistance and/or jump training, have also been observed for both prepubescent[79-81] and early pubertal girls[79, 82, 83]. MacKelvie

and colleagues, however, did not observe the improvements at the hip and spine in prepubertal girls that were observed in early pubertal girls in response to brief high impact exercise[84].

5.1.2.4. Post-puberty

Few exercise interventions have been completed with acutely postpubertal adolescents. Following eight months of plyometric and jumping exercise in an adolescent female cohort (mean age = 14.2 yrs, approximately 2 years past menarche), no significant difference between intervention or control groups was observed at any bone site, with the exception of an increase in trochanteric bone mineral content in the exercisers[85]. Because the trial was not randomized and controls were highly active, it was unclear whether the lack of response was due to the high level of activity in controls or if adolescent bone does not respond as dramatically to increased loading as prepubertal bone. Another trial reported fifteen months of resistance training produced a significant increase in femoral neck bone mass in adolescent girls (roughly 2.5 years post menarche), despite major challenges with subject compliance[86]. A study comparing the effects of twice weekly step aerobics for 9 months in pre- vs. postmenarcheal girls reported bone mass and geometric parameters of bone strength increased at the spine and hip for premenarcheal girls only[87].

Thus, in support of cross-sectional findings, data from intervention trials suggest exercise has a very positive effect on bone mass and geometry in children. The consensus suggests the effect is most marked in the years just prior to or during early puberty. It remains to be seen if those benefits translate to a reduced risk of osteoporosis and/or fracture in later life. Only large, very long-term follow-up investigations can determine if such an objective will be realized.

5.2. Exercise and bone mass in adults

Although, the response of the adult skeleton to exercise has been studied extensively, the considerable logistical challenges and methodological inconsistency associated with exercise trials may account for the diversity of findings. Randomization is particularly difficult, as adults who volunteer for an exercise study do not wish to be allocated to a control group. Innumerable studies are casualties to poor compliance, given the necessarily protracted duration of interventions, and poor acceptance of exercise by those who often need it most. Furthermore, there are relatively few studies of men due to the common misperception that osteoporosis is a disease unique to women.

5.2.1. Adults, exercise and bone - Cross-sectional observations

Observational data indicate that adults engaged in weight-bearing exercise at intensities of >60% of aerobic capacity have consistently greater bone mass than non-exercisers or those exercising at low aerobic intensities. These differences have been observed in the whole body[88-96], spine, proximal femur[56, 88-91, 93, 95-104], pelvis[90, 94], distal femur[105], tibia[88, 90, 102, 106, 107], humerus[90], calcaneus[108, 109], and forearm[102]. Broadband ultrasound attenuation and speed of sound transmission in the calcaneus are similarly higher in runners than controls[93]. Consistent with the principle of specificity, high bone mass is typically observed local to the loaded bone(s)[94, 110-112].

Certain activities do not sufficiently overload the skeleton to cause an adaptive response[113]. Athletes participating in moderate to high intensity impact activities such as running, jumping and power lifting have greater bone mass than those performing low intensity or non-weight bearing activities[92, 104, 114, 115]. By contrast, individuals who participate in non-weight bearing activities such as swimming have similar bone mass to non-exercisers[105, 116], although some data to the contrary exists for men[117]. Muscle forces on the skeleton during elite-level swimming

training do not appear to offset the substantially reduced daily weight bearing activity associated with long periods of time spent in a weight-supported environment (water).

In non-exercising adults, as in children, the dominant arm exhibits greater total and cortical bone mass than the non-dominant arm[68, 118] and side-to-side differences are exaggerated when the dominant limb is chronically overloaded[69, 70, 98, 105]. Some have found the difference is accounted for by increased periosteal area and cortical thickness rather than bone mass[118], while others have observed both expanded diaphyseal diameters and increased bone mass in the dominant limb of athletes. Dalen and associates[69] observed a 27% difference in cortical cross-sectional area between left and right humeri of tennis players compared to a non-significant 5% difference in controls. Krahl and colleagues[119] observed differences in diameter *and* length of playing arm ulnae of tennis players compared to the contralateral arms. The second metacarpals of playing hands were also wider and longer than those of the contralateral hands, whereas no differences were observed between limbs of controls. The latter somewhat isolated observations suggest that exercise may potentiate long bone growth in length, a curious finding with implications for overall height. That side dominance is not evident in athletes who load both limbs equally in the course of their training (rowers and triathletes)[120] attests to the principle of site specificity.

Although data exists to question the role of exercise in the prevention of age-related bone loss[121], there is no denying that active people who have exercised for many years, generally have higher bone mass than less active people[58, 91, 97, 122-125 126]. Unfortunately, while bone loss may be reduced by lifelong exercise, it may bear little or no relationship to the incidence of fractures. For example, Greendale and colleagues[125] reported a significant linear trend in older men between both lifetime and current exercise and hip bone mass, but found no relationship between

osteoporotic fracture rate and exercise history. The paradox could be related to other risk factors for falling and the lack of a persistent neuromuscular benefit from early life exercise.

5.2.2. Exercise interventions in young and mature premenopausal women

Randomized, controlled trials confirm that exercise training programs enhance the bone mass of young women in a site-specific manner. Both resistance and weight-bearing endurance exercise programs increase spine, hip and calcaneal bone mass of young adult women[45, 127-131]. However, in contrast to the developing skeleton, the principle of reversibility applies, that is, osteogenic loading must be sustained in order to maintain bone gains. For example, increases in trochanteric and femoral neck BMD observed after 12 months of resistance plus jump exercise declined to baseline values after only six months of detraining in premenopausal women[132] (Figure 3). Two-year observations of college gymnasts indicate that bone at the hip, spine and whole body consistently increased over the training seasons and decreased in the off-season[133] (Figure 4). By contrast, the relatively lower magnitude loading associated with field hockey playing was not sufficient to stimulate seasonal changes in a similar cohort[134].

Based on an awareness of the importance of load magnitude and rate for bone stimulation, researchers have frequently employed impact loading (jumping) as an exercise intervention. While load magnitude is similar for jogging and jumping (2-5 times body weight), the loading rate for jogging is roughly 75 body weights/second while jumping is approximately 300 body weights/second. Commensurately, jumping has consistently been shown to increase femoral and sometimes lumbar spine bone mass in premenopausal women[34, 45, 127 135-137]. Curiously, number of reported impacts performed per session in the studies describing a bone effect range from a low of 10[135] to a high of 100[138, 139]. Direct comparisons among studies to evaluate a dose-response of bone to jump number are thus clouded by variance between training protocols,

varying age of participants, and the lack of accurate information with respect to impact exposure (other aerobic activity).

Few studies have addressed the skeletal response to loading in the years just prior to menopause. The limited data suggests that perimenopausal women who exercise will maintain bone mass at loaded sites to a greater extent than those who do not[140, 141].

5.2.3. Exercise interventions in postmenopausal women

The reduction in circulating estrogen and associated acute and rapid bone loss that accompanies menopause represents a powerful confounding factor for the study of exercise effects on bone at this time. Furthermore, combining both early and late postmenopausal women in exercise trials will obscure the factor imparting the most profound effect, exercise or estrogen. Even those investigations specifically targeting estrogen-deplete early postmenopausal women have reported inconsistent findings with respect to the ability of exercise to prevent bone loss at all sites. Resistance training effectively maintained only spine bone mass in some cases[142 143], and only trochanteric bone mass in others[30]. A rare finding that walking prevented hip bone loss, an effect that was enhanced by isoflavone intake, was recently reported in a cohort of early postmenopausal Japanese women[144]. High-intensity resistance training was as effective as hormone therapy in preventing bone loss at the spine and was more effective than no hormone therapy in attenuating bone loss at the spine in women an average of two years post menopause[145]. A four-year progressive strength training program found exercise frequency to be significantly positively associated with changes in bone mass at the hip and spine in women an average of six years post menopause regardless of hormone therapy status[146].

Resistance training programs of nine to twenty-four months duration in estrogen-deplete late postmenopausal women are generally associated with an increase or maintenance of bone mass

compared to losses in controls at the whole body[41], lumbar spin [41, 42, 142, 147-149], proximal femur[29, 42, 148, 149], calcaneus[149] and radius[29], although not without exception[150-152]. A recent meta-analysis of high intensity resistance training and post menopausal bone loss concluded that high-intensity resistance training confers a significant positive effect on spine bone mass but that findings are highly heterogeneous at the femoral neck[153]. Significant changes at the hip were observed only in trials that recruited subjects not taking hormone therapy. Exercise effects were augmented with calcium supplementation and in women with low initial values. The authors also remarked on the poor methodological quality of studies, that non-randomized trials report markedly greater treatment effects than randomized, and that reporting bias towards studies finding positive bone outcomes was evident.

The most clinically relevant sites are primarily comprised of trabecular bone, thus cortical bone is often ignored in research trials. As long bone fractures indeed occur at cortical sites in osteoporotic individuals, an observation that both resistance and agility training increased cortical bone density in elderly osteopenic women is of clinical relevance[154]. Although substantial changes in femoral neck bone mass were not observed, tibial shaft bone strength index was maintained to a greater extent in elderly women performing one year of resistance and balance-jumping training than in controls[155].

Weight bearing aerobic or impact exercise interventions of seven to thirty months duration are also generally associated with increases or maintenance of bone mass compared to losses in control subjects at the whole body[41, 156], lumbar spine[33, 40, 143, 156, 157], proximal femur[41, 156, 158], radius[157] and calcaneus[159, 160].

As for other groups discussed previously, lower intensity activities typically do not promote bone gain or reduce loss in postmenopausal women. A 12 month, 5 d/wk, 45 min moderate-

intensity aerobic exercise intervention did not provide sufficient overload to the skeletons of obese postmenopausal women to improve bone mass[161]. Similarly, 12 months of unloaded exercise in waist-deep water did not prevent spine bone loss or improve femoral bone mass in osteoporotic women, despite changes in other functional fitness parameters[162]. It is generally agreed that walking alone is not an effective strategy for osteoporosis prevention in postmenopausal women[163]. Exceptions include the above-mentioned Japanese study and a report by Hatori and colleagues[40] who found that seven months of walking 3 d/wk at walking speeds equivalent to those reached in race walking (>4.5 mph) increased lumbar spine bone mass in postmenopausal women. The increased muscular forces associated with arm movements required for walking at high speeds combined with lower initial bone mass values might explain these isolated positive responses.

Unfortunately, high magnitude loading is not appropriate for individuals with osteoporosis whose bones would likely fracture under such loads. It has been observed, however, that lower magnitude loading may be osteogenic if applied at high enough rate and/or frequency (roughly 30 Hz). While the active application of loads at frequencies higher than 2-3 Hz is not physically feasible for most, whole body vibration (WBV) devices have been developed that can apply passive, low magnitude loads at osteogenic frequencies. Preliminary findings of the effectiveness of WBV to enhance bone strength are encouraging[164-168], however, as WBV is primarily a passive rather than active stimulus, it cannot strictly be considered exercise, and will not be discussed further.

The length of participation in weight bearing exercise may be an important consideration for exercise programming in older adults. For example, although no change in femoral neck bone mass was observed in post menopausal women following nine months of jump plus resistance

exercise wearing weighted vests[169], 5 years of participation in the program prevented bone loss of more than 4% at the hip[35] (Figure 5). It is possible the delayed response is a function of mineralization, a process known to continue long after new bone tissue (osteoid) has been secreted by osteoblasts.

Given the importance of site-specificity, it is not surprising that weight bearing exercise does not increase forearm bone mass in postmenopausal women[41, 137]. In fact, some have suggested that upper body bone mass may suffer at the expense of lower body bone mass in female runners[170]. For those at risk of Colles (distal forearm) fractures, however, it is encouraging to observe that upper extremity loading of high rate and magnitude, stimulated higher forearm bone density in osteoporotic, postmenopausal women after only five months[171, 172].

5.2.31. Hormone therapy and exercise

As hormone therapy (HT) has been a common treatment for postmenopausal symptoms and side effects in the past, the efficacy of exercise in comparison to, and in combination with HT has been examined. In some reports, exercise enhanced the bone maintenance effect of HT. Resistance exercise has been shown to significantly increase spine, hip, total body and radial mid-shaft bone mass menopausal women who were estrogen-replaced compared to maintenance effects observed in estrogen-replaced, non-exercising controls[173, 174]. Similarly, the interaction of HT and nine months of weight bearing exercise (walking, jogging, stairs) resulted in greater increases in total body and lumbar spine bone mass in 60-72 year old postmenopausal women than exercise or HT alone[175].

By contrast, other studies report no interaction between exercise and HT. For example, a 3 hr/wk program of resistance exercise plus walking or running for one year did not enhance the positive effect of estrogen supplementation on lumbar vertebral or femoral neck bone mass in

postmenopausal women[176]. Similar results were observed at the lumbar spine and hip in early postmenopausal women on HT, despite a positive effect of 3 hr/wk exercise on bone mass in a placebo group[177]. In these studies, a longer intervention period and higher load magnitudes may have been necessary for more positive outcomes. Somewhat perplexingly, given the usual site specific effect of bone loading, Judge and colleagues observed changes in total hip bone mass in postmenopausal women on long term hormone therapy regardless of randomization status to either upper body-only or lower body-only resistance training[178]. The investigators concluded that any kind of moderate resistance exercise in the presence of hormone therapy conferred a generalized positive effect at the hip.

5.2.4. Exercise interventions in young adult men

Although there have been few longitudinal studies in this cohort, the response of the male skeleton to exercise appears to be similar to that of same-aged women.

Basic military training has served as an opportune model to observe the effect of brief, high intensity, multi-mode, physical training interventions. After 14 weeks of basic training, male army recruits have been observed to improve calcaneal strength[179], and increase leg bone mass by around 12%; those with the lowest initial values gaining the greatest amount[106, 180]. Recruits who temporarily stopped training due to stress fracture also gained bone mass, but to a lesser degree (5%). Curiously, 10% of the same recruits lost bone mass. The latter effect may have been a function of either incomplete remodeling owing to the short observation period, or abnormal remodeling due to fatigue and inadequate rest intervals.

The influence of training intensity on bone response becomes evident when findings from army trials are compared with those of recreational athletes. By contrast to recruits, men aged 25-52 failed to gain bone at the spine, humerus, femur, calcaneus or forearm following three

months of either walking (three kilometers, five days a week) or running (five kilometers, three days a week)[114]. The disparity of findings likely reflects the novelty of loading and higher load magnitudes experienced during basic training, and the youth of the army recruits. The only other young male exercise intervention to have been reported involved nine months of marathon training. The investigators observed significantly higher calcaneal bone mass in the runners than non-runners with a positive association between average distance run and percent change in bone mass[159].

A 7.8 year longitudinal study of young Caucasian men (mean age = 17 years) measured change in bone mass over time according to change in level of activity[181]. The investigators reported those men who stayed active gained bone mass, those who ceased activity lost bone mass at the hip, but remained significantly higher than controls at final follow up. The study is an illustration of the ability of exercise to potentiate male peak bone mass even in the very final stages of skeletal growth.

5.2.5. Exercise interventions in older adult men

There are even fewer reports of exercise interventions with older men. From a combined male and female trial, Welsh and Rutherford[156] reported a significant increase in trochanteric bone mass in six men aged 50-73 years who performed twelve months of step and jumping exercise. More recently, the effects of six months of either a high-intensity, standing, free-weight program or a moderate-intensity, seated, resistance training program on bone mass was examined in older men and women[30]. High intensity training increased lumbar spine BMD by 2% in the men (mean age = 54.6 years), whereas moderate intensity training produced no change. Increased bone mass was observed at the greater trochanter regardless of training intensity.

5.3. Summary of exercise effects across the lifespan

Evidence from exercise interventions longer than six months indicates that activities of high magnitude and rate of loading improve bone mass and geometry in children and adults of both sexes. While gains may be maintained if achieved during the growing years, adults will likely lose new bone if exercise is discontinued. Effective activities include jumping and high intensity weight training. Although walking and other low intensity exercises are unlikely to be substantially osteogenic, a lifetime of walking appears to be beneficial to the skeleton.

6. CALCIUM AND EXERCISE.

The permissive action of calcium in enhancing the effect of exercise on bone mass is somewhat controversial. In a review of seventeen trials, Specker[182] concluded that an intake of 1000 mg per day of calcium is necessary in order to observe a skeletal response to exercise. Specifically, the evidence suggests that the combination of calcium supplementation and exercise is more effective for a bone response in children[183 74, 184], adolescents[185] and postmenopausal women than calcium supplementation alone[33, 39, 186].

By contrast to the positive reports, a recent cross-sectional study of 422 women found that even though high levels of physical activity and calcium intake were associated with a higher total body bone mass than low activity levels and low calcium intake, there was no significant interaction between exercise and calcium[95]. Furthermore, two years of combined aerobics and weight training increased bone mass in young women, but calcium supplementation neither enhanced the exercise benefit, nor improved bone mass in the absence of exercise[128].

Although exercise likely provides a greater stimulus to bone than does calcium, at least in older children and adults, adequate calcium intake is recommended, particularly in children, to provide the building blocks for exercise-induce gains in bone mass.

7. HORMONE RESPONSE TO INTENSE EXERCISE

7.1 Women

Exercise-associated amenorrhea occurs in some premenopausal women who train at high exercise intensities. While low body fat was once thought to precipitate exercise-associated amenorrhea, it is now thought that reduced energy availability disrupts the hypothalamic-pituitary-thyroid axis[187], and ultimately circulating reproductive hormones. The effect of reduced energy availability on bone resorption and formation markers is well documented[188]. The reduction in estrogen provides the link between exercise-associated amenorrhea and bone loss[113, 189, 190]. The Female Athlete Triad describes the combined conditions of excessive dietary restraint, reproductive hormone disturbance and bone loss in female athletes.

The question of whether the Triad should be considered a pathological or even psychopathalogical condition has recently become contentious[191-193]. What is generally accepted is that in all but cases of extreme (high magnitude) loading, the positive effect of exercise on bone cannot offset the negative effects of inadequate energy availability during high intensity, high volume exercise training. To illustrate, gymnasts load their skeletons at very high magnitudes and rates, and thus, despite a high prevalence of menstrual disturbance, have bone mass well above normal[194]. Long distance runners, on the other hand, who load their skeletons at much lower rates, are not protected from amenorrhea-related bone loss. Although there are individual differences, the loss of bone mass in amenorrheic distance runners increases their risk of stress fracture and premature osteoporosis compared with their eumenorrheic running counterparts[195]. Loucks and co-workers suggest that exercise-associated amenorrhea may be prevented or reversed by increasing energy consumption, without alterations in training[196].

There is some suggestion that oral contraceptives (OC) may offset bone loss in athletes with menstrual dysfunction, but there are insufficient data to fully corroborate the effect[197]. Keen and Drinkwater[198] reported that initiating OC use approximately eight years after the onset of athletic oligo- or amenorrhea did not improve bone mass, concluding that intervention should begin at the onset of dysfunction in order to prevent significant loss. The effect of OCs, alone or in combination with exercise, on bone strength indices is, however, poorly understood. In fact, for women aged 18-31 years, exercise alone and OCs alone depressed normal age-related increases in femoral neck mass and size, although the combination of exercise and OC was slightly less detrimental[199]. It is likely that a complex interaction of factors yet to be identified will account for these puzzling findings.

7.2. Men

Intense training is not associated with commensurately severe alterations in reproductive hormones in men. Male athletes exercising at a range of intensities have serum concentrations of testosterone that lie within the normal range[107, 108, 120, 200, 201] including adolescents[202]. In some athletes, however, a degree of subtle hormonal perturbation can occur. Smith and Rutherford[120] reported that, although in the normal range, serum total testosterone was significantly lower in triathletes than controls, but not rowers. Further, total serum testosterone, non-sex hormone binding globulin (SHBG)-bound testosterone, and free testosterone concentrations in men running more than 64 kilometers per week was 83%, 69.5% and 68.1% that of controls, respectively[203]. Others have similarly observed that resting and free testosterone concentrations of trained athletes are 68.8% and 72.6% that of controls[204]. Age may influence the effect as elderly endurance athletes have significantly greater levels of SHBG than controls whereas younger athletes demonstrate no differences compared to controls[108, 205].

Whether hormones potentiate the effect of exercise on bone in men is relatively unexamined. Suominen and Rahkila[108] reported a negative correlation between bone mass and SHBG in older endurance athletes but no relationship of bone mass with testosterone. Further, the addition of self-administered anabolic steroids (testosterone: 193.75 +/- 147.82 mg/week) to high intensity body building training does not stimulate greater osteoblastic activity or bone formation than exercise alone[206]. Four months of progressive resistance exercise training four d/wk, with or without growth hormone supplementation, did not significantly increase whole body, spine or proximal femur bone mass in elderly men (mean age = 67) with normal bone mass[207]. Similarly, the addition of recombinant human growth hormone to six months of resistance exercise training, induced no change in bone mass of older men[208, 209].

8. OSTEOPOROTIC FRACTURE AND FALLS

8.1. Fracture and exercise

Exercise studies that include fractures as an outcome measure are difficult and expensive to conduct. Very long term follow up of interventions is required and many men and women at risk for fracture due to poor bone health are on pharmacological therapy that can mask the effect of exercise. In general, the literature supports a protective effect of physical activity on the risk of fracture, especially at the hip[210-213]. Specifically, the Study of Osteoporotic Fractures, a large, prospective, community-based, observational study of healthy, older, Caucasian women, reported that moderately to vigorously active women had significantly fewer hip and vertebral fractures compared to inactive women[210]. Similarly, data from the Nurse's Health Study showed that moderate levels of activity, including walking, were associated with a significantly lower risk of hip fracture in postmenopausal women[214]. Two studies that tracked fractures over a prolonged period of exercise[215] or over a follow-up period after completion of an exercise intervention[216]

suggest a protective effect of exercise against fracture. The incidence of vertebral fractures was lower (1.6%) eight years after a two-year back extension exercise program compared to controls (4.3%)[216]. Original exercisers had better back extension strength at follow-up and a 2.7 lower relative risk of vertebral compression fracture than controls.

8.2 Falls and exercise

Falls are the cause of almost 90% of all hip fractures[217 218, 219]. As previously indicated, exercise can affect both the numerator and denominator of the factor of risk. Discussion thus far has focused on exercise as a means of altering the denominator of the factor of risk, that is, on increasing fracture load by improving parameters of bone strength. However, exercise can also reduce the numerator either by preventing a fall entirely or by lowering the applied load of falls through improved neuromuscular responses.

Risk factors for falls are numerous, and some can be modified by exercise. Lateral instability, muscle weakness of the lower extremities, and poor gait have been found to independently predict hip fracture and falls[220-223]. Impaired balance is similarly related to incidence of vertebral fracture[224]. In the Study of Osteoporotic Fractures in Men, men in the upper quartile of leg power and grip strength had a 18%-24% lower risk of falls compared to men in the lowest quartile[225]. Since exercise promotes and maintains muscle strength, balance and mobility, it is an intuitive strategy for reducing osteoporosis-related fractures[226, 227]. In fact, muscle strengthening and balance training have been shown to reduce extraskeletal risk factors for hip fracture in elderly men and women[228, 229] and overall risk of falling by as much as 75%[229, 230]. That vibration superimposed on muscle training exercise augments the strengthening effect[231] suggests whole body vibration may be a preventative strategy with dual (anti-fall and bone building) benefits.

A 30-month randomized controlled trial of high-impact exercise in 160 elderly women with low bone mass reported a lower incidence of fall-related fractures among exercisers compared to controls, despite minimal effects on hip bone mass[215]. Improvements in neuromuscular function resulting from low intensity exercise, including water-based exercise[155, 232, 233], while not osteogenic, may likewise be efficacious for fall and fracture prevention.

Exercise interventions with falls and injurious falls as primary outcomes are limited but tend to support the role of exercise as a preventative strategy. Data from the FICSIT trials (Frailty and Injuries: Cooperative Studies of Intervention Techniques) indicate that activities that are most beneficial for reducing incidence of falls include those that result in muscle strength gains and dynamic balance improvements[234]. Lord and coworkers[235] reported improvements in strength and balance in elderly women but no change in incidence of falls after twelve months of exercise that included resistance, and a similar null effect on falls after an individualized prevention program that included exercise[236]. Yet, other trials by the same group reported a reduction in falls among the elderly who participated in group exercise in both community-dwelling[237] and retirement home[238] settings. Campbell[239] found that a multifactorial exercise intervention involving muscle building plus walking exercise reduced injurious and non-injurious falls by 40% in elderly women. The study required home visits by physical therapists and it is not known which component of the program, muscle building, walking, or the two combined, was most potent for reducing falls.

Sadly, the fall reducing benefit of exercise may not extend to the very frail elderly[240-243] despite improvements in fall risk factors and physical function[240, 242]. Trends toward lower falls among exercisers, however, were apparent in studies of longer duration[242, 243], suggesting that a longer period of adaptation may be required to detect protective effects in this population.

9. RECOMMENDATIONS: EXERCISE PRESCRIPTION

9.1. The Osteogenic Index – an exercise algorithm derived from animal data

Charles Turner has translated the findings of a generation of basic animal research into a theory for practical exercise application[244, 245]. With Alex Robling, he developed the Osteogenic Index (OI), a method to predict the effectiveness of an exercise regime to improve parameters of bone strength based on the known response of bone cells and tissue to certain types of loading[245]. The OI requires dynamic (cyclical) loading, and accounts for load magnitude, rate and frequency[246 29, 41, 131, 247, 248]. They note that animal bone tissue becomes desensitized to prolonged loading stimuli and, in fact, loses the majority of its mechanosensitivity after twenty loading cycles[49, 249] Adding rest periods between bouts of loading markedly improves the bone response to a cyclical stimulus[250]. Thus, they propose that a regime of frequent, short, intense bouts of exercise should be most beneficial to bone.

The validity of the Osteogenic Index for human application remains to be tested. Preliminary evidence suggests the human response may vary in subtle ways, such as the importance of cycle number. For example, while 300 jump repetitions per week for seven months produced positive effects at the hip and spine in prepubescent children, reducing the jump number to 150 failed to reproduce the effect[251]. Collective findings of jumping studies in premenopausal women, however, support the OI theory as even low numbers of weekly jumps can produce a bone response with little added benefit from additional impacts[44, 135 138, 139]. Recently, it was reported that women who performed the greatest amount of impact activity, measured by accelerometry, above a threshold level of intensity had significantly greater improvements in hip BMD compared to women who performed lower amounts of activity[252]. These data suggest that the

cycle number may be an important determinant of bone responsiveness to impact activity, but that the effect may follow more of a threshold rather than dose response pattern.

9.2. ACSM Position Stand – recommendations based on human data

Based on the best evidence to date, recently American College of Sports Medicine published a Position Stand for Physical Activity and Bone Health[253] with the following recommendations. Children should engage in 10-20 minutes (split into two sessions if possible) of high intensity activities that include jumping-type activities at least three times a week. Adults should engage in 30-60 minutes of a combination of weight bearing endurance of moderate to high intensity, jumping 3-5 times per week and resistance exercises targeting all major muscle groups 2-3 times per week. Prolonged immobilization and bed rest should be avoided at all costs, given the very negative effect of unloading on bone mass and the limited ability to fully regain losses with remobilization.

While high magnitude (impact) activities are recommended for increasing bone mass of the younger, more robust skeleton, they are not recommended for those with advanced osteoporosis. In the frail elderly population, particular care must be taken to maintain a balance between safety and efficacy since the exercise intervention itself (through increasing activity levels) presents not only the possibility of skeletal and neuromuscular benefit, but also an increased risk of fracture. Osteoporotic individuals, with or without a history of vertebral compression fractures, should not engage in jumping activities or deep forward trunk flexion exercises such as rowing, toe touching and full sit ups. Through a combination of dynamic force analyses at the hip and spine and ex-vivo measurements in cadaveric bone, it is possible to determine the factor of risk for most of the exercise activities that might be used in exercise studies in the elderly. Understanding and maintaining a safe value of the factor of risk for a specific exercise program is crucial. Until

such understanding is achieved, caution is warranted in the use of overload concepts in the frail elderly. Before initiating a program of high intensity, elderly individuals should consider a bone density evaluation. Any individual undertaking a new program should begin slowly with careful attention to exercise form and appropriate progressions. Exercises that produce severe joint pain or muscle soreness of more than three days should be discontinued until exercise of lower intensity can be tolerated.

10. FUTURE RESEARCH

The large body of research data notwithstanding, in fact it remains impossible to say without reservation that exercise will reduce the likelihood of fracturing. As Karlsson has stated, much of the research has been "hypothesis generating" rather than "hypothesis testing"[254] – a consequence of the confounding challenges associated with exercise RCTs and the protracted nature of follow up required to compare real fracture rates between exercise and control groups. Indeed, while much has been achieved in our understanding of the use of exercise for the prevention of age-related fractures, many questions and challenges remain. For instance we know little about the relative importance of mechanical, endocrine and genetic factors and how these interact to potentiate or blunt the exercise response in bone over the life span. How these mechanisms relate to the temporal sequence of the bone remodeling cycle is also unclear.

It is likely that the complex interplay of genetics, nutrition, hormone status, and even a degree of central control[255] accounts for much that remains unexplained about the bone response to exercise. That mechanical loading cannot entirely prevent spinal cord injury-related bone loss[6] is testament to the presence of influences yet to be explained.

Thus, while the power law model incorporating load magnitude and number of repetitions of Whalen and colleagues[256] and the Osteogenic Index of Turner and Robling[257] have moved us

forward in our ability to design and test exercise regimes for bone health, a definitive exercise prescription remains elusive. The challenge remains to identify a means by which optimal overload can be determined in order to safely stimulate a positive bone response. The complex interplay of dose (load magnitude and rate), cycle number and duration must be elucidated in human models. Only then can we customize exercise prescription for bone with confidence.

Finally, it is important to consider the issue of compliance. The commitment to regular exercise of any kind, much less the relatively specific form required to effect change in bone, is known to be challenging for the vast majority of individuals. Compliance even with study protocols, when volunteers often have access to state-of-the-art facilities and personnel to encourage and support their efforts, is routinely disappointing. For example, compliance of a mere 17.8% was reported for an 18-month, home-based, exercise program for the prevention of postmenopausal osteoporosis, primarily due to lack of motivation[258]. Few maintain a lifelong exercise routine, and those who do are unlikely to vary their regime the extent required to stimulate ongoing bone adaptation. In reality, the greatest challenge for bone physiologists may not be the identification of the optimal exercise program, but the engagement of the community to utilize the knowledge. In this respect, the health of the skeletal system shares commonality with the cardiovascular and neuromuscular systems.

11. CONCLUSIONS

Regular physical activity has the potential to reduce the risk of osteoporosis and fragility fractures by: 1. optimizing peak bone mass, 2. consolidating or maintaining adult bone, and 3. reducing the risk and incidence of falls. As each strategy is age-specific, exercise prescription for the prevention of osteoporosis-related fractures will differ across the lifespan.

Exercise will only effect bones that are loaded during the activity. Bone requires substantial overload for prolonged durations for positive adaptations to be stimulated. With the possible exception of the pediatric population, bone gains will likely be lost if a stimulatory exercise is discontinued. Individuals with the weakest bones can expect the greatest improvements from initiating exercise. Exercise is most efficacious when accompanied by adequate calcium consumption.

Exercises that are most or least likely to substantially alter bone mass and prevent falls can be identified with relative certainty. Development of individualized and population-specific exercise prescription across the lifespan is more challenging. Issues such as determining actual bone strain exposure during activity, optimal dose response, safety, and the interaction of exercise with pharmacology remain opportunities for future research. It will be important to determine the degree to which exercise-invoked improvements in bone strength and falls prevention will translate to a reduction in incidence of fracture.

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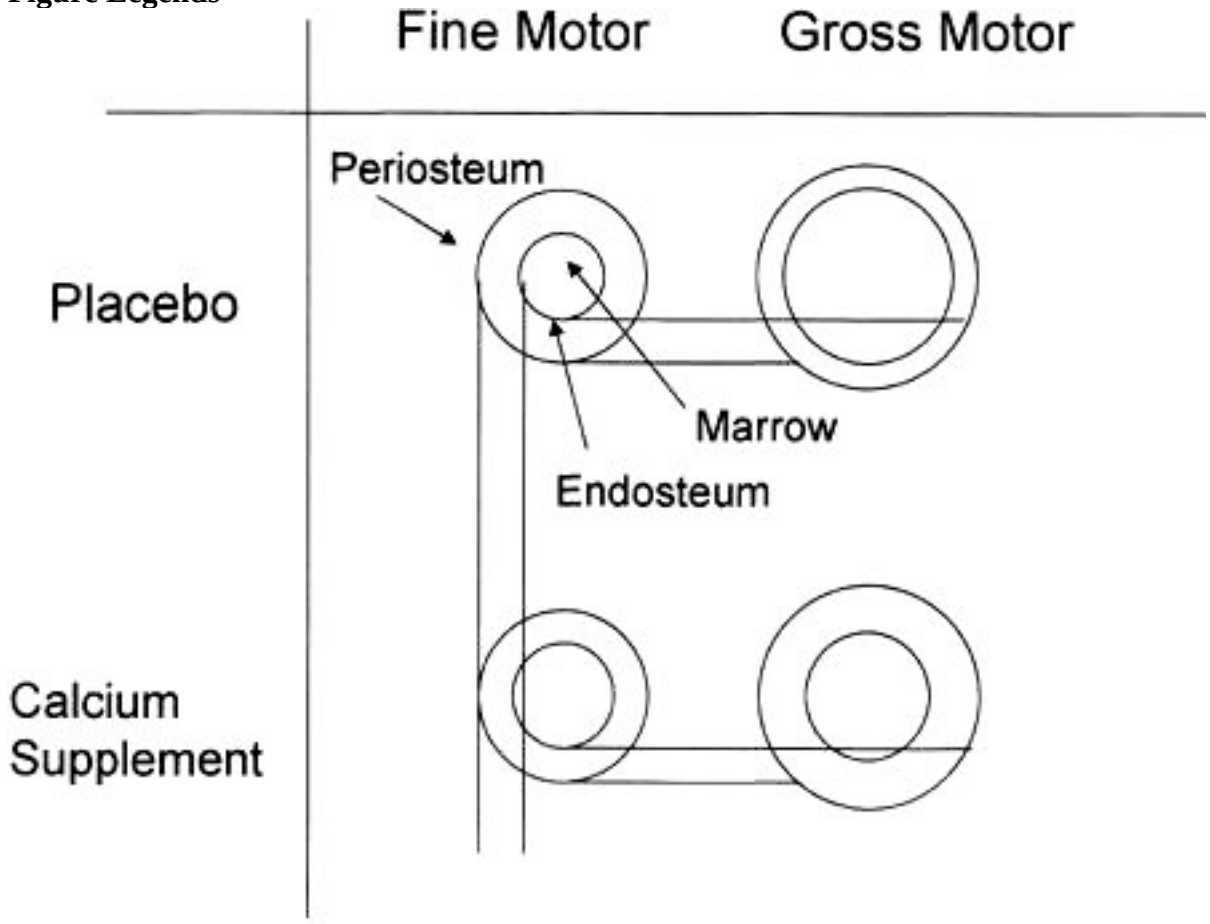
Figure Legends



Diagrammatic illustration of the effects of physical activity and calcium intake on a cross-section of the 20% distal tibia shaft by pQCT in young children (not to scale).

Figure 1. Diagrammatic representation of the effects of 1 year fine motor or gross motor activities and calcium supplementation on the cross section of the 20% distal tibial shaft by pQCT in young children (not to scale). (Reproduced from *Journal of Bone and Mineral Research* 2003;18:885-892 with permission of the American Society for Bone and Mineral Research.)

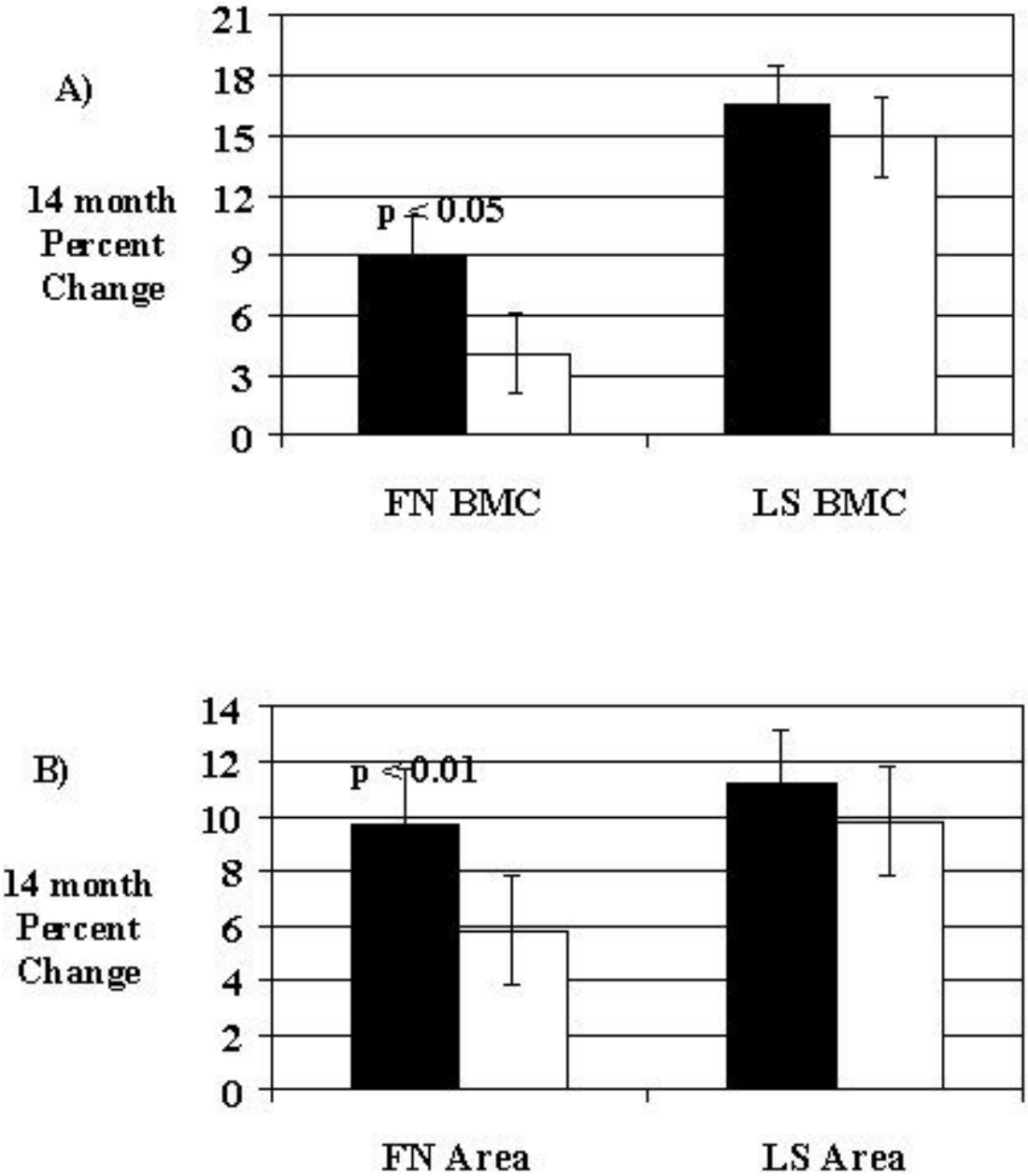
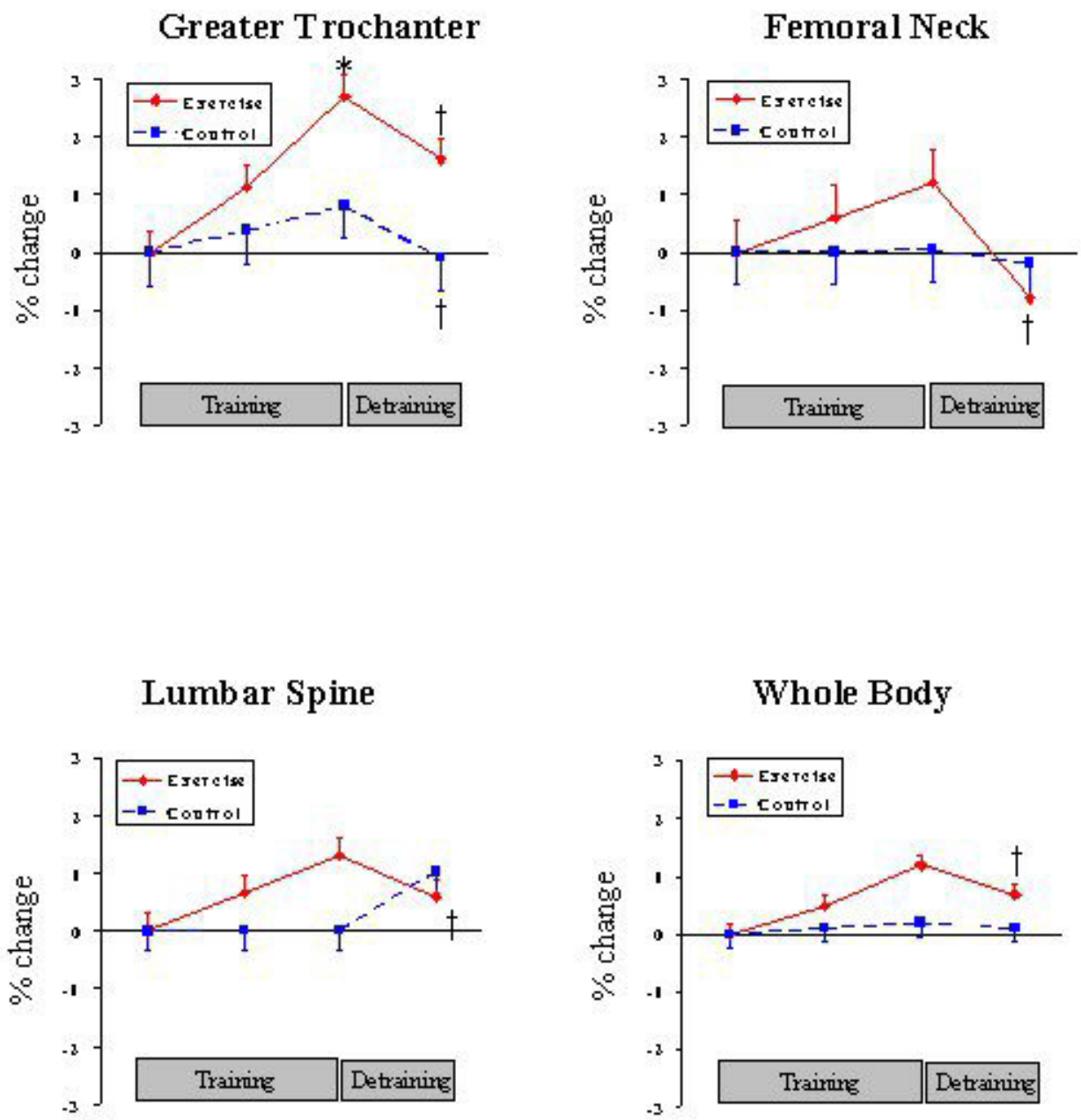


Figure 2. A. 14-month changes (exercise intervention plus detraining) in femoral neck BMC were significantly greater ($p<0.05$) in jumpers (n=37, black bar) than controls (n=37, white bar). No-significant differences were observed between groups for lumbar spine BMC. B. 14-month changes (exercise intervention plus detraining) in femoral neck area were significantly greater ($p<0.01$) in jumpers (n=37, black bar) than controls (n=37, white bar). No-significant differences were observed between groups for lumbar spine area. Values reported as percent change (%), mean ± SEM. (Reprinted from *Journal of Pediatrics*, 141, Fuchs RK and Snow CM, Gains in hip bone mass from high-impact training are maintained: A randomized controlled trial in children, pages 357-362, copyright (2002) with permission from Elsevier.)



* = exercise group significantly different from controls, $p<0.05$

† = change over detraining period significantly different from change over training period, within groups, $p<0.05$

Figure 3. Percent changes in BMD across training and detraining periods (mean ± SEM) at the (A) greater trochanter, (B) femoral neck, (C) lumbar spine, and (D) whole body. (Reproduced from *Journal of Bone and Mineral Research* 2000;15:2495-2503 with permission of the American Society for Bone and Mineral Research.)

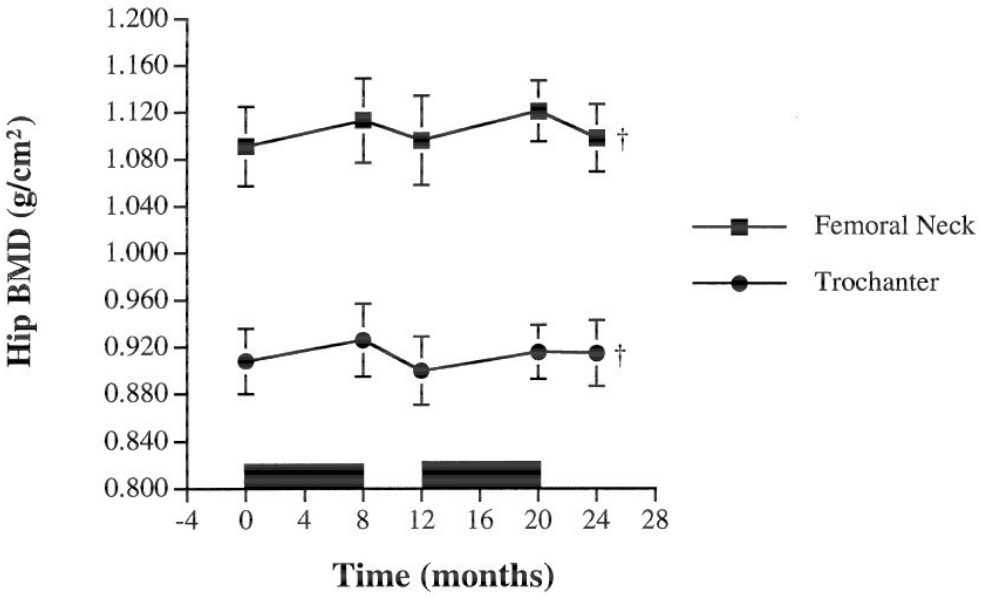


Fig. 4. Changes in hip BMD over 24 months in intercollegiate gymnasts. The dagger (†) represents a significant quartic seasonal trend for repeated increases and decreases in hip BMD at the femoral neck ($P = 0.028$) and trochanter ($P = 0.031$) in the group of eight gymnasts. Black bars indicate the timing of the competitive training seasons. Data are expressed as mean ± SEM.

Figure 4. Changes in hip BMD over 24 months in intercollegiate gymnasts (n = 8). The dagger represents significant quartic seasonal trends for repeated increases and decreases in hip BMD at the femoral neck and trochanter (p = 0.03). Black bars indicate the timing of the competitive training seasons. Data are expressed as mean ± SEM. (From *Calcified Tissue International*, 69, 2001, 7-12, Bone gains and losses follow seasonal training and detraining in gymnasts. Snow CM, Williams DP, LaRiviere J, Fuchs RK, Robinson TL, Figure 4, with kind permission of Springer Science and Business Media.)

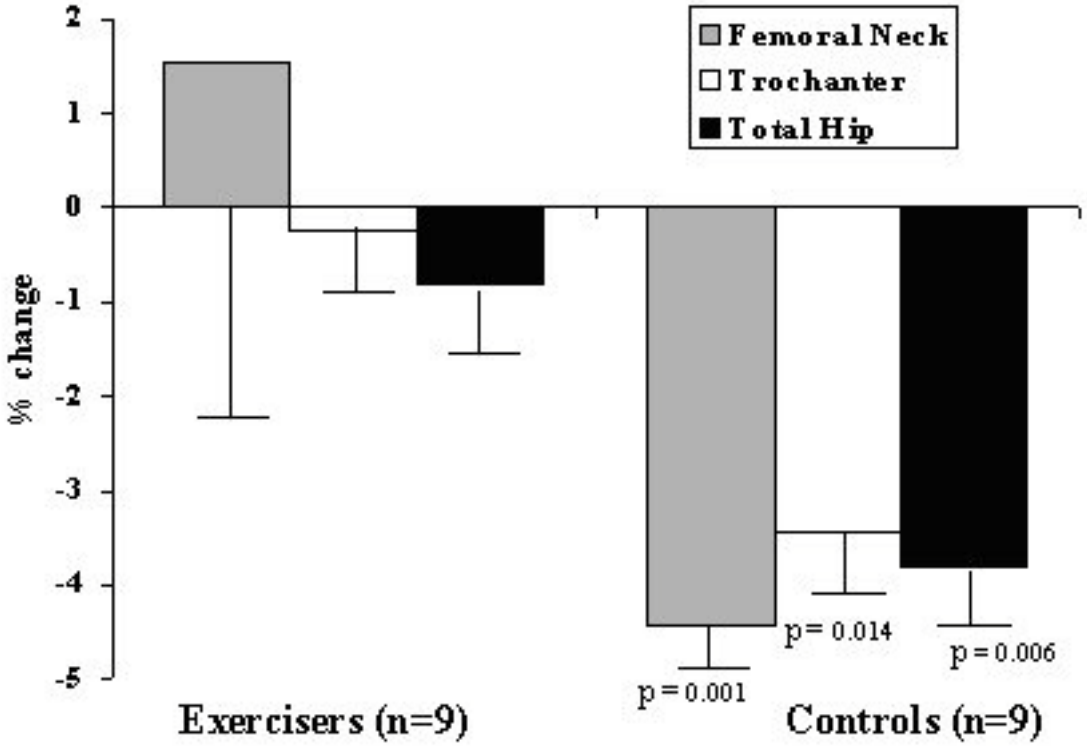


Figure 5. Percent changes in BMD at the femoral neck, trochanter and total hip in exercisers and controls after 5 years. Changes for exercisers were 1.54% ± 2.37 (CI = -3.9 to 7.0%) at the femoral neck, -0.24 ± 1.02% (CI = -2.6 to 2.1%) at the trochanter and –0.82 ± 1.04% (CI = -3.2 to 1.6%) at the total hip, whereas controls decreased 4.43 ± 0.93% (CI = -6.6 to -2.3%) at the femoral neck, 3.43 ± 1.09% (CI = -5.9 to -0.92%) at the trochanter and 3.80 ± 1.03 (CI = -6.2 to -1.4%) at the total hip. Decreases in controls are significantly different from zero (unpaired t-tests). Data are presented as means ± SEM. (From Snow CM, Shaw JM, Winters KM and Witzke KA, "Long-term exercise using weighted vests prevents hip bone loss in postmenopausal women." *Journal of Gerontology: Medical Sciences*.55A(9):M489-M491,2000. Copyright © The Gerontological Society of America. Reproduced by permission of the publisher.)