PERSPECTIVES

Exercise During Growth: Compelling Evidence for the Primary Prevention of Osteoporosis?

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Abstract

Exercise during growth is widely recommended as a key strategy in the primary prevention of osteoporosis. This theory seems reasonable if exercise is pursued into adulthood, but perhaps not if exercise is ceased; in the latter case, the mechanostat theory predicts a decrease in bone strength due to a decrease in the largest forces applied to the skeleton. However, recent findings suggesting maintenance of bone strength after exercise cessation contradict the mechanostat theory. Former elite athletes display greater bone mass and bone strength than age-matched controls despite several years of retirement (i.e., several years of reduced loading). Recent animal studies that investigated the effects of detraining on bone strength also support this view. As many confounders can modulate bone strength during the period of detraining, these observations need further support before they can be validated. There is still not enough evidence to ascertain confidently that the skeletal benefits obtained during growth can be maintained into old age, and that these benefits are large enough to reduce the risk of fracture at a population level. *BoneKEy.* 2007 June;4(6):171-180.
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Introduction

Increasing peak bone density is a key strategy in the primary prevention of osteoporosis: a 10% higher peak bone density is associated with a 50% lower risk of fracture and theoretically delays the onset of osteoporosis by 13 years (1;2). Exercise during growth has been shown to lead to large increases in bone mass (3) and the biomechanical strength of bones (4;5) – much greater than achieved at any other time of life. However, the benefits obtained during growth are only of clinical significance if one hypothesizes that they are maintained into later life when fragility fractures occur. Testing this hypothesis in humans is very challenging due to the long time frame between exposure (exercise in childhood) and outcome (fracture in older age). This leaves us with lower levels of evidence to develop a case that the benefits of exercise are maintained. In addition, the large changes observed during growth have generally been observed in young athletes who have been involved in intense training programs over many years. More moderate exercise programs over 1 to 2 years have resulted in far more conservative responses in normally active children (see (6) for a recent review). Thus before exercise during growth can be recommended in the primary prevention of bone fragility, a compelling case must be developed to show not only that the benefits are maintained, but that they will be large enough to be considered clinically important at a population level.

Rationale: The Role of Peak Bone Strength in the Primary Prevention of Osteoporosis

One strategy to increase bone strength in late adulthood – and thus decrease the risk of fracture – is to maximize peak bone strength attained during growth. Periosteal bone apposition is a cardinal feature of skeletal development (7). Growing bone must continually adjust its strength to increases in body weight, bone length and muscle forces to keep strains (bone deformation) within the threshold range for modeling and remodeling (7). By accruing bone on the periosteum, the skeleton

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maximizes the strength bone can attain for a given amount of bone mass because bending strength increases as radius to the power of 4 (8). Exercise during growth has the capacity to increase bone strength through impact loading and, most importantly, through muscle forces that dominate the skeleton's postnatal structural adaptation to loading (9-12). This is demonstrated by the greater bone size, bone mass and bone strength observed at loaded sites in young athletes (4;5;13;14) (Figure 1).

The question is: can these structural adaptations obtained during growth remain intact until senescence? Intuitively this would seem unlikely, particularly if exercise is reduced or ceased in adulthood (15). According to the mechanostat theory, whatever the initial bone strength may have been during early adulthood (i.e., increased due to exercise during growth), bone strength late in adulthood will be just as strong as it takes not to be damaged under the usual voluntary loads. Former elite athletes are thus expected to have similar bone strength as non-athletes of the same age, provided that they are currently experiencing similar levels of physical activity (Figure 1, Hypothesis #1).

There is some evidence, however, to suggest that this may not necessarily be true. In former elite gymnasts aged 18-35 years who had retired for 8 years after 10 years of high-intensity training, bone mass was significantly greater at all loaded sites compared to age-matched controls, despite complete cessation of gymnastics training (16). Further investigations with peripheral quantitative computed tomography (pQCT) revealed that the greater bone mass found in the retired gymnasts was associated with greater bone size, cortical cross-sectional area (CSA) and trabecular volumetric density in the upper limbs (humerus and radius), and greater CSA and trabecular volumetric density at the tibia (unpublished data). Despite experiencing similar levels of exercise as the controls (no more than two hours per week of regular physical activity since retirement), the former gymnasts still had stronger bones (Figure 1, Hypothesis

#2). A selection bias cannot be excluded; the retired gymnasts may have had stronger bones before starting gymnastics. However, the risk of having such a bias is likely to be limited because the retired gymnasts were matched for age, height, weight, total body lean mass and fat mass with the controls.

Due to the cross-sectional design of the study, it was not possible to determine whether or not the gymnasts had lost bone mass and bone strength after retirement. In a situation of reduced loading (exercise cessation in adulthood), bone loss can theoretically occur through bone resorption on the periosteal surface (reduction in bone size) or on the endosteal surface, resulting in reduced cortical CSA (endocortical resorption), increased cortical porosity (intracortical resorption) or trabecular thinning (resorption on the trabecular surface). The mechanostat theory does not inform us about which mechanisms truly occur. But according to the aforementioned findings, and without ruling out potential bone loss, it seems that the retired gymnasts maintained, at least partly, the structural adaptations obtained during growth.

Similar findings have been reported in a prospective study conducted with pQCT in former national-level tennis players. Significant side-to-side differences in bone size, cortical area and bone strength index were reported after 1.5 to 3 years of retirement (17). The marrow cavity was larger, not smaller, in the playing arm, suggesting that the players had greater endocortical expansion during activity or that bone loss occurred on the endocortical surface after retirement.

These observations give support to the theory that the structural adaptations obtained during growth may remain intact until senescence (18-20). This can be explained by the fact that the mature skeleton is thought to lose bone mass essentially through remodeling on the endosteal envelope, and to a much lower extent on the periosteal envelope, thereby preserving bone size (7;21-25).
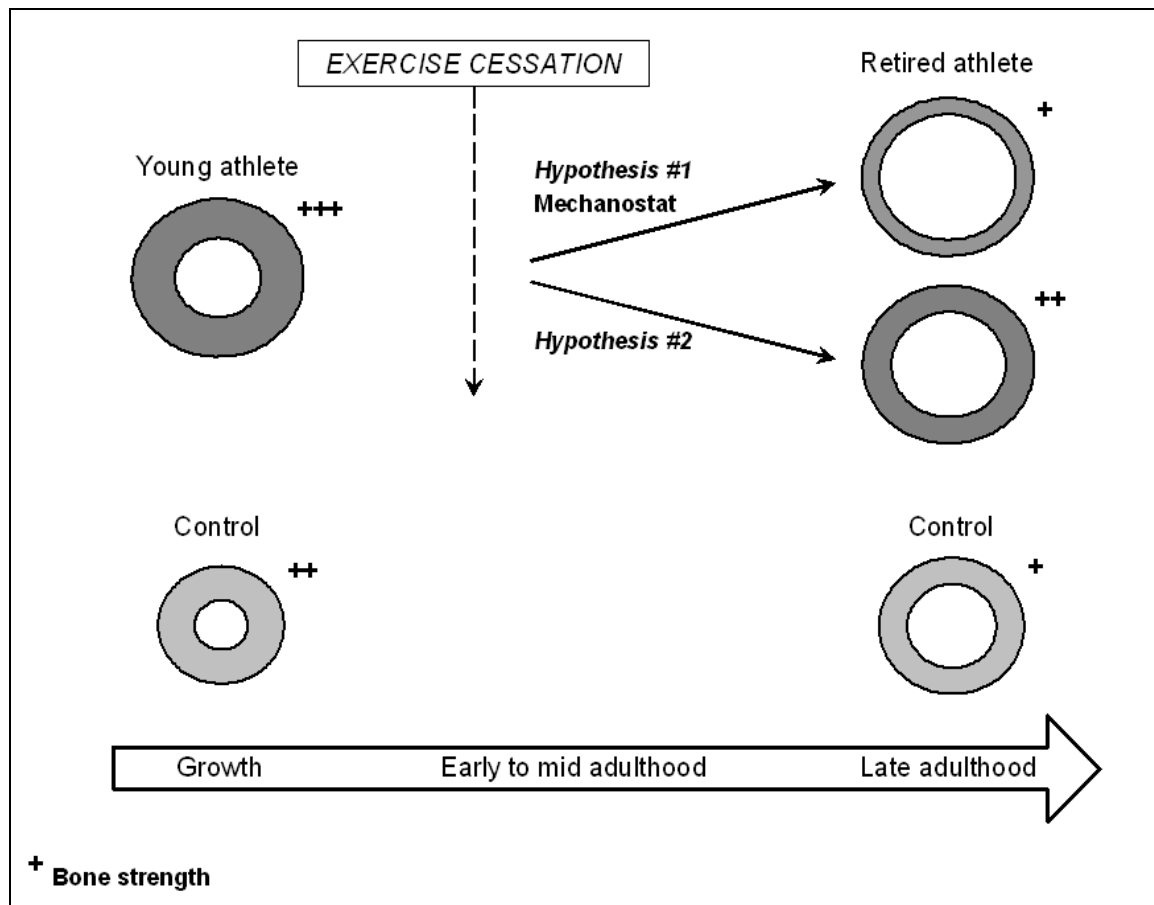
Figure 1. Is Bone Strength Maintained into Late Adulthood Despite Exercise Cessation? Exercise during growth is associated with an increase in bone mass that is predominantly translated into an increase in bone size. As a consequence, young athletes have bigger and stronger bones than age-matched controls (*left*). According to the mechanostat, bone is constantly adapting its strength to its loading environment via modeling and remodeling through a controlled mechanical feedback system. Therefore, one would expect that exercise cessation in early- to mid-adulthood is accompanied by a reduction in bone strength matching the reduction in loading. The reduction in bone strength is unlikely to be obtained by a reduction in bone size because the mature skeleton adapts its strength predominantly through remodeling. As a consequence, retired athletes may still have bigger bones in late adulthood but with relatively less bone mass than sedentary age-matched controls (Hypothesis #1, *right*). There is limited evidence, however, to suggest this may not be the case. Recent investigations with peripheral quantitative computed tomography (pQCT) in former gymnasts who fully retired 8 years ago revealed that the skeletal sites that were submitted to high loads during growth still showed a greater bone mass, and most importantly greater bone size and cortical cross-sectional area (CSA) in the upper limbs (humerus and radius) and greater cortical CSA and trabecular volumetric density at the tibia (unpublished data). If these benefits can be maintained despite aging, the retired gymnasts will reach late adulthood with stronger bones than their age-matched counterparts (Hypothesis #2, *right*).

Nevertheless, the retired athletes included in the aforementioned studies were younger than 40 years of age. To what extent aging can alter the skeletal benefits retained by mature bones that were subjected to high loads during growth remains unknown. Studies in senior tennis players (age > 55 years) showed that the playing arm had greater bone mass and bone strength. No conclusion can be reached from this result, however, because these senior players had remained active (26;27). It is thought that apposition of bone on the periosteal surface partly counteracts the endosteal resorption that occurs with aging. The rate of periosteal expansion has been shown to remain stable in elderly men, while it is progressively reduced in elderly women (24;28). Further

investigations are needed to determine the mechanisms of bone loss in aging retired athletes. Does periosteal expansion occur in this population, and can it counteract bone loss on the endosteal surface? Is the magnitude of periosteal expansion similar between long bone shafts and the epiphyses that are rich in trabecular bone? Do retired athletes have thicker trabeculae than age-matched non-athletes? Addressing these issues is critical before confidently asserting that elderly individuals who exercised during growth display stronger bones than lifelong sedentary peers.

Does Exercise During Growth Result in Reduced Fragility Fractures in Old Age?

While the primary prevention of osteoporosis is often focused around increasing areal bone mineral density (aBMD), the most important clinical outcome is to reduce fracture incidence. Results of retrospective fracture studies of former athletes are equivocal. After the age of 35 years (after retirement), the proportion of subjects with fractures (evaluated by questionnaire) was lower in 663 former elite athletes (age range: 50-93 years) than in 943 age-matched controls (8.9% versus 12.1%, respectively) (29). After the age of 50 years, fewer retired athletes than controls sustained fragility fractures (2.3% versus 4.2%, respectively) (30). In contrast, the fracture incidence was not different between 284 former soccer players (mean age 64 years) and 568 controls (2.1% vs 3.7%, respectively) (31). Nor was there any difference in the lifetime occurrence of fractures between 2622 former female college athletes and 2776 non-athletes, from the age of 21 to 80 years (32).

There could be several reasons why these results are conflicting. The timing, volume, intensity and duration of training of the athletes are likely to have a significant influence on the results. In particular, did the training take place in the pre-, peri- or post-pubertal phase of growth? Were these individuals elite athletes who trained for extended periods during the growth phase or were they recreational athletes who participated in training twice a week with a game on the weekend? In this study design,

sampling bias cannot be discounted; would the athletes have had a lower fracture rate even if they had not been involved in exercise during growth? Was there a total cessation of exercise on retirement, or was there maintenance of some level of exercise? How active were the controls? Were the controls comparable across all groups, in terms of exercise during leisure and work? Can we assume that the response to exercise and the maintenance of the benefits is comparable between sexes? We know that there is sexual dimorphism in skeletal growth and aging. There is also limited evidence that the skeletal adaptation to exercise is sex-specific (33-35). Is the ability to maintain the benefits also sex-specific? Finally, the ability to detect the difference in fracture incidence is difficult in any study because of the large sample size needed for adequate statistical power to confidently reject the null hypothesis – that there is no difference in fracture incidence between retired athletes and controls. Thus the efficacy of exercise during growth to reduce fracture incidence in aging cannot be determined with any confidence from the available literature.

Does Exercise During Growth Result in Greater Bone Strength in Adulthood?

In the absence of quality data on the effect of exercise on fracture risk, the next approach is to determine if exercise during growth influences bone parameters related to bone strength during aging. As mentioned before, very few studies have investigated the maintenance of bone strength after exercise cessation, and the results were focused on former elite athletes (retired gymnasts, unpublished results, retired tennis players (17)). In the general population, one retrospective study was conducted with quantitative computed tomography (QCT) and reported that men who were involved in impact training during growth but who stopped in adulthood did not show any significant difference with the control group in terms of bone geometry and estimated bone strength at the mid-femur (36).

Other levels of evidence come from studies which used aBMD as a surrogate of bone strength. In one of the longest follow-ups (27

years, from the age of 13 to 40), men who participated in impact training during growth but not in adulthood had similar aBMD at the lumbar spine and whole body as men who had been sedentary or involved in non-impact sports since childhood. In contrast, 12% higher spinal aBMD values were found in men who participated in impact sports during growth and maintained this activity in adulthood (37).

In athletes retired for 10 to 20 years, it has been reported that aBMD at loaded sites is maintained at about 0.5-1.0 standard deviations above the age-predicted mean (16;38-43). These findings are not consistent, however, because there are several studies that report no detectable benefit being maintained (39;44) (Table 1).

Discipline	Age of the retired athletes (years)	Duration of training (years)	Duration of retirement (years)	aBMD (g.cm^{-2}) in retired athletes
Tennis (17)	~30	~20	1-3	Dominant arm > Nondominant
Soccer, Ice Hockey (30)	16-37	~15	5	Above age-matched controls
Gymnastics (16)	18-35	4-8	1-20	Above age-matched controls
Gymnastics (43)	20-32	5-12	3-12	Above age-matched controls
Soccer (55)	34-84	Not provided	5-20	Above age-matched controls
Tennis, Running (42)	40-65	15-20	~15	Above age-matched controls Dominant arm > Nondominant arm in former tennis players
Gymnastics (56)	36.1 ± 3.5 45.3 ± 3.3	~10	15 24	Above age-matched controls "
Weight lifting (39;40)	35-49 50-64 65-79	Not provided	25 ± 13	Above age-matched controls Above " Not different from controls
Soccer (31;44)	17-85	1-30	5 16 25 >35	Above age-matched controls Above " Above " Not different from controls
Ballet dancing (57)	51 ± 14	9.5 ± 5.5	1-53	Not different from controls

Table 1. Long-term Effects of Exercise During Growth on Areal Bone Mineral Density (aBMD) at Loaded Sites: Evidence in Retired Athletes. Descriptive data are reported as minimum-maximum values or as mean ± standard deviation if the range was not provided.

The statement that continued activity, even at low intensity, is needed to maintain some of the benefits cannot be validated because of the paucity and limitations of the existing data. The difficulty for adults in recalling their level of physical activity in youth introduces

considerable inaccuracy in retrospective studies. In addition, neither aBMD nor bone geometry are perfect surrogates for bone strength, which is determined by bone material and structural properties (45). Thus, the evaluation of bone strength is still very

challenging *in vivo*. Three dimensional techniques like QCT, pQCT and magnetic resonance imaging (MRI) have opened a new era in the investigation of skeletal fragility by taking bone macro-architecture into account. However, no long-term prospective study has ever been conducted with such methods. Applications of these techniques to evaluate bone quality (notably trabecular bone microarchitecture) are still in development.

Many of the difficulties encountered in human investigations can be overcome in animal studies, since the measurement of bone strength is easier, the entire lifespan can be covered within the same experiment, and the modalities of training and detraining can be controlled. Preliminary results of animal studies are contradictory. Detraining over periods from 4 to 15 weeks showed the maintenance (46-48) or loss (49) of the training-induced changes in bone strength. A longer follow-up revealed that although the geometric changes were partly maintained 14 weeks after the cessation of exercise (50), they eventually disappeared after 42 weeks of detraining (51). After a longer training program (11 months versus 14 weeks in (51)), preservation of the increased bone volume and bone mineral content was observed in mice, even twelve months after the cessation of exercise (52). Two-year-old horses that were trained during 8 months had an increase in bone size of the third metacarpal bone. Bone size and resistance to bone deformation were still increased (although not significantly) after 5 months of detraining (53).

The positive results reported in several studies can be explained partly by the fact that the animals were still growing during the detraining period (46-48;53). Continuous growth, which is associated with an increase in body weight, represents an osteogenic stimulus that may have helped to maintain the skeletal benefits throughout the detraining period. In addition to this limitation, bone strength, which is the main outcome, was assessed with different protocols (compression test (48;51) or three-point bending test (46;51)), making the comparison between studies difficult. The discrepancies in the results can also stem from the large variety of training programs (treadmill running (47-49;51;52), jumping (46), race horses' training (53)) and corresponding skeletal sites that were investigated (spine (52), tibia (46-49), femur (47;51), humerus (47;48) or metacarpal bone (53)).

In a recent study, the right forearms of young female rats were subjected to a 7-week training, followed by a 92-week detraining (54). A within-subject comparison between the loaded forearm and its non-loaded counterpart showed that the exercise-induced changes in bone quantity did not persist after detraining (BMC and aBMD by DXA); however, there was long-term maintenance of exercise-induced bone structural changes. After detraining, exercised ulnas had 23.7% greater ultimate force, which was associated with a relatively small increase in bone size (+4.4% only in cortical area) but a 25% increase in the minimum second moment of inertia I_{MIN}, reflecting a change in bone shape to better withstand loading. The exercised ulnas also showed a 10 times greater fatigue resistance after detraining, but also an increased brittleness.

This study did not require a control group, which is a major advantage. However, the investigations were conducted with a relatively small number of rats (10 out of the 32 originally included) and the animals were still gaining weight after exercise cessation. Moreover, the ulna axial compression model is supposed to generate the same strain pattern as engendered during *in vivo* axial loading, but the absence of muscle hypertrophy on the loaded side contradicts that point. Because such models do not involve any actions from the muscles and tendons surrounding the loaded bone, it may not be a good surrogate of normal physical activity. Overall, findings obtained in animals cannot be directly translated to the aging skeleton.

Conclusion

There is weak evidence in humans supporting the contention that skeletal benefits obtained from exercise during growth are maintained into old age despite

exercise cessation. Confounding factors (e.g., a healthy lifestyle adopted during youth and pursued in adulthood) may have contributed to some positive findings. The mechanostat theory, which is frequently cited to describe the skeletal adaptation to loading, has a limited capacity to explain the changes in modeling and remodeling that occur on the periosteal and endosteal surfaces. In addition, most studies investigated the effects of detraining after intense training. Would we find skeletal benefits in older adults who exercised at a moderate level during youth? How many fewer fractures in the elderly will result from a community-based exercise campaign in children? Our inability to answer these questions should be acknowledged before recommendations are made at the community level. Dose-response studies are needed to determine which minimum threshold of exercise during growth is necessary to obtain an increase in bone strength that is clinically significant (6) and which minimum threshold of exercise during adulthood is necessary to maintain the skeletal benefits and prevent osteoporosis (51).

Conflict of Interest: The authors report that no conflicts of interest exist.

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