

Does exercise during growth influence osteoporotic fracture risk later in life?

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The reduction in bone strength associated with aging and resultant increase in the risk for low trauma fracture represents a prominent and growing problem. Interventions that increase bone strength and reduce the risk for fracture are highly desirable. Although numerous pharmacological agents have been developed to prevent and treat reductions in bone strength, a commonly advocated intervention is the prescription of exercise. Bone is a mechanosensitive tissue that responds and adapts to its prevailing mechanical environment. Exercise that increases mechanical loading results in increases in bone strength, whereas removal of mechanical loading causes bone strength to decrease. While this ability of bone to respond to mechanical stimuli has been known for over a century, the clinical importance of the response continues to be a matter of debate.

Reduced bone strength is predominantly an age-related phenomenon, increasing with age. However, the ability of the skeleton to respond to mechanical loading decreases with increasing age. Thus, exercise does not appear suited at offsetting the decrease in bone strength associated with aging. Reflecting this, the introduction of exercise to the adult skeleton has been met with variable success in modifying bone mineral density (BMD), a surrogate measure of bone strength. In comparison, the immature skeleton is unequivocally more responsive to mechanical loading. In fact, the skeletal benefit of a lifetime of exercise occurs mainly during the years of skeletal development. This has created a so called 'window of opportunity' during pre- and early puberty where the skeleton is most amenable to the

influences of mechanical stimuli. The presence of this window has most eloquently been shown in studies of racquet-sport players. Players who began their playing careers during pre- and early puberty had more than two-fold greater differences in bone mineral content (BMC) between their playing and non-playing arms, compared to those who began playing post-puberty¹. The disparate response of the skeleton to mechanical loading with aging and the reduction in bone strength with age has raised the question of whether exercise-induced bone changes during growth persist into adulthood where they would be most advantageous.

Bone mineral density changes induced by loading are not maintained long-term

Exercise during growth adds extra material to loaded sites to increase BMD. By adding more bone when young the skeleton may be primed to offset the bone loss associated with aging. Initial clinical trials have demonstrated that training-induced changes in BMC and BMD are maintained at least in the short-term following the cessation of training²⁻⁵. Similarly, a number of animal studies have demonstrated that loading-induced changes in BMC and BMD persist with a detraining period of equal length to the exercise period^{6,7}.

While exercise effects persist short-term following the cessation of exercise, they do not appear to persist long-term where they would be advantageous in reducing bone fracture risk⁸⁻¹⁶. Karlsson et al.¹⁷ demonstrated that while exercise (soccer playing) in youth conferred a high peak BMD, cessation of exercise resulted in accelerated BMD loss during aging, with exercise benefits being lost after 10-20 years of retirement. Supporting this, Järvinen and colleagues¹³ demonstrated in an animal model that BMD changes induced by exercise during growth were lost with a detraining period double the duration of the training period. Consequently, it appears that exercise-induced changes in BMD during growth are not maintained long-term following the cessation of exercise.

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DXA is limited in assessing the maintenance of loading-induced bone changes

While changes in BMD appear to be lost following the cessation of exercise, this does not mean that exercise-induced changes in bone strength do not persist into adulthood where they may have anti-fracture benefits. Previous studies investigating the long-term benefits of exercise on the skeleton used dual energy X-ray absorptiometry (DXA) to assess bone status. While DXA undoubtedly provides a reasonable picture of overall bone status, it has significant limitations in the assessment of bone strength and the determination of fracture risk. This is because DXA is inherently planar in nature and has low-spatial resolution. These factors do not allow DXA to provide an adequate measure of bone structure.

Bone strength, and the consequent risk for fracture, is dependent upon not only how much bone is present but also the distribution of this bone (structure). DXA only provides measures of the former and not the latter. Because of this, DXA-derived measures are not sole predictors of bone strength and fracture risk. Meta-analysis of the effects of osteoporosis drug therapy confirm this with DXA-derived BMD explaining only a fraction of the observed reduction in the risk for fracture¹⁸. As DXA does not assess bone structure, it is particularly limited when assessing bone changes (and their maintenance) induced by mechanical loading. Mechanical loading predominantly influences bone structure rather than mass to impact bone strength.

Mechanical-loading predominantly influences bone structure and strength

Mechanical loading generates large increases in bone strength without substantial increases in bone mass as it causes new bone tissue to be placed where mechanical demands are greatest. This has been most clearly demonstrated using the rat ulna axial loading model. In this model, the right forearm is axially loaded across the olecranon and flexed carpus. The ulna is the major load-bearing bone in this model carrying two-thirds of the applied load. The load on the ulna is translated mostly into a bending moment which accentuates the bone's mediolateral curvature to generate strains and consequent adaptation on the medial and lateral surfaces. As the mediolateral plane in the rat ulna corresponds with the minimum second moment of area (I_{MIN}), bone adaptation in this model predominantly causes an increase in I_{MIN} . I_{MIN} is a structural property and refers to the distribution of bone mineral around the plane of least bending rigidity. By mechanically testing the bones in the same direction as they were adapted, we have found that very small increases in bone mass generated very large increases in its mechanical properties^{19,20}. The importance of bone structure to skeletal mechanical properties was further reflected in these studies by high correlations between structure (I_{MIN}) and bone mechanical properties ($r^2 > 0.76$).

Bone structural and strength changes induced by loading may be maintained long-term

As bone structure influences bone strength, exercise during growth could have long-term anti-fracture benefits via the structural changes it induces, independent of any long-term effects on bone mass. Exercise during growth positively alters bone structure by causing new bone to be preferentially laid down on the periosteal (outer) surface of the bone, as is evident by enhanced periosteal expansion^{21,22}. As bone loss during aging occurs primarily on the endocortical surface and not the periosteal surface²³, this enhanced structure during growth may remain intact until senescence where it may have anti-fracture properties. Few studies have investigated this. Three animal studies^{6,7,24} have shown that exercise-induced changes in bone cross-sectional area are maintained short-term following the cessation of exercise (equal duration of detraining to training). However, these studies did not investigate long-term benefits. In another animal study, Järvinen and colleagues^{13,25} demonstrated running during rodent growth to increase femoral neck cross-sectional area. This benefit persisted for a detraining period of equal length to the training period; however, it was lost after a period double the duration of training¹³. The reported reason for this loss was an apparent catch-up phenomenon wherein the bones of the control rats caught up the bone gain of the exercised rats with age and concomitant growth. However, this study was limited by the use of a between-animal study design. We currently have a within-animal, longitudinal study investigating the long-term benefits of mechanical loading during growth on bone structure. Pre-pubertal (five-week-old) rats were mechanically loaded for seven weeks using the ulna axial compression model to induce adaptation. With a detraining period of over one-year, the bone structural (I_{MIN}) changes induced by loading remain consistent. There is no indication of a 'catch-up' phenomenon, and indications are that the changes persist long-term. As I_{MIN} is significantly correlated with bone mechanical properties, this data suggests that loading-induced changes during growth may have lasting benefits on bone strength and consequent fracture risk. This hypothesis is supported by recent clinical data that demonstrated former athletes to have a lower fracture risk than controls²⁶.

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