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Exercise, Hormones, and Skeletal Adaptations During Childhood and Adolescence

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Abstract

Although primarily considered a disorder of the elderly, emerging evidence suggests the antecedents of osteoporosis are established during childhood and adolescence. A complex interplay of genetic, environmental, hormonal and behavioral factors determines skeletal development, and a greater effort is needed to identify the most critical factors that establish peak bone strength. Indeed, knowledge of modifiable factors that determine skeletal development may permit optimization of skeletal health during growth and could potentially offset reductions in bone strength with aging. The peripubertal years represent a unique period when the skeleton is particularly responsive to loading exercises, and there is now overwhelming evidence that exercise can optimize skeletal development. While this is not controversial, the most effective exercise prescription and how much investment in this prescription is needed to significantly impact bone health continues to be debated. Despite considerable progress, these issues are not easy to address, and important questions remain unresolved. This review focuses on the key determinants of skeletal development, whether exercise during childhood and adolescence should be advocated as a safe and effective strategy for optimizing peak bone strength, and whether investment in exercise early in life protects against the development of osteoporosis and fractures later in life.

Keywords

bone; exercise; estrogen; testosterone; IGF-1; children; adolescents

Osteoporosis: A Major Public Health Problem

Osteoporosis is a common skeletal fragility syndrome that typically manifests in old age and poses a major threat to public health, contributing to enormous medical, social and economic costs that will worsen with our growing elderly population (60). Indeed, >10 million

Americans are affected by osteoporosis (60), and >33 million more have osteopenia (ie, low bone mass) which often leads to osteoporosis. Shockingly, the number of Americans with low bone mass could reach 61 million by 2020 (46). Left unchecked, the 2 million osteoporotic fractures reported in 2005 could exceed 3 million in 2025, with costs rising from \$16.9 to \$25.3 billion annually (7). While skeletal prophylaxis is primarily prescribed to the elderly population, given the dire projections, perhaps the time has come to encourage safe and effective nonpharmacological interventions in youth to combat this problem. With that in mind, this review focuses on whether exercise during childhood and adolescence should be advocated as one such strategy and whether investment in exercise early in life protects against the development of osteoporosis and fractures with aging.

Is Osteoporosis A Pediatric Concern?

Although mainly considered a disorder of the elderly, emerging evidence suggests the antecedents of osteoporosis are established during childhood and adolescence (16,63), which manifest into diagnosable problems much later in life. In fact, peak skeletal accrual is now widely recognized as an important determinant of adult bone health status (23). In addition to biochemical and hormonal changes, altered loading environments during growth resulting from increases in body mass, more powerful muscles, and rapid gains in height are critical factors that determine peak bone acquisition (23). The significance of the peri-pubertal years for establishing peak bone health is emphasized by the observation that in the two years surrounding peak linear growth, over 25% of skeletal mass is accrued (2). This is as much bone mass as women will typically lose from 50 to 80 years of age (26), which may also be true in men (31). Puberty is a time of rapid bone modeling adaptations that alter bone structure and ultimately increase the strength of bone independent of bone mass (56). Thus, the peripubertal years are now recognized as the most opportune period to modify bone structure and strength, traits that tend to track throughout life (16,63). As such, there is considerable interest in understanding how modifiable factors are causally implicated in enhancing bone health during growth.

Determinants of Bone Strength

Bone strength is ultimately determined by its material composition and the arrangement of bone tissue in space (ie, geometry; 56). A long bone of the appendicular skeleton needs to be light to facilitate movement, yet stiff and flexible to resist deformation, absorb energy, and keep strains imparted by biomechanical stimuli within a safe range (17). If bone is too stiff or too flexible, it will crack under conditions of loading resulting in fracture. The unique material composition and structural design of bone serves the contradictory needs of stiffness versus flexibility and lightness versus strength (56).

Stages of Physical Maturation and Endocrine Events During Puberty

Physical maturation is an important consideration in pediatric studies because chronological age does not adequately capture the timing of hormonal changes that take place during puberty. Children at the same initial stage of development can advance through puberty at different rates and the timing and trajectories of changes in hormonal factors are known to differ greatly between sexes. For these reasons, the range in physical maturation between

girls and boys of the same chronological age can be quite wide. Consequently, studies that aim to understand skeletal health in youth must assess the physical maturation of the participants and carefully account for the variability in physical maturation in analyses.

Currently, the gold standard for assessing pediatric skeletal maturation is bone-age, which can be obtained from plain x-rays of the hand and wrist (ie, radius-ulnae small bones) using the RUS-TW3 method developed by Tanner and Whitehouse (57). Because the subject is exposed to the radiation inherent to the technique, most pediatric studies rely on Tanner staging. Typically, this involves a self-report questionnaire that presents illustrations of five advancing pubertal development stages representing either female or male secondary sex characteristics (ie, breasts [girls], genitalia [boys], and pubic hair [girls and boys]). Accordingly, Tanner Stage I is defined as prepubertal, Tanner Stages II and III are defined as early pubertal, Tanner Stage IV is defined as late pubertal, and Tanner Stage V is considered fully mature. In girls, menarche is typically reached during Tanner Stage III. While Tanner staging is common in pediatric studies and has been shown to agree well with physical examination and grading of sexual maturation by trained medical personnel (43), its ability to accurately assess maturity is limited because of the subjective self-report nature of the method. Because of this limitation, a number of prospective studies have applied an alternative approach whereby longitudinal anthropometric measures of height are taken for several years surrounding puberty to capture peak height velocity (PHV), which in essence represents a common biological landmark that can be used to control for the maturational differences among peri-pubertal girls and boys of the same chronological age (2). Application of this method requires longitudinal follow-up of at least three years (41). Recognizing that many studies cannot meet this requirement, Mirwald and colleagues (42) developed sex-specific algorithms to extrapolate a maturity offset value based on cross-sectional anthropometric measures of height, sitting height, leg length, and body mass. This method has been shown to agree well with Tanner staging and longitudinal measures of PHV.

While none of the aforementioned techniques for assessing physical maturation are perfect, these methods have been shown to relate with changes in estrogen (E), testosterone (T), insulin-like growth factor 1 (IGF-1), and growth hormone (GH) throughout puberty in both girls and boys (33–35). For example, levels of IGF-1 and GH are low in boys and girls during prepuberty and both hormones increase transiently during midpuberty. However, because puberty occurs earlier in girls as compared with boys, these hormones rise and peak at earlier ages in girls relative to boys; similarly PHV and peak bone mineral accrual velocity typically occur about 1.5 years earlier in girls than boys (41). Generally, secretion of GH increases by ~1.5 to threefold during midpuberty, and this is accompanied by a greater than threefold increase in IGF-1 levels (41). Increases in GH are also stimulated by E in girls and T in boys (41,62), which both rise gradually throughout puberty with changes occurring earlier in girls as compared with boys (41). T particularly favors abdominal fat deposition and muscle accrual (18,50). Comparatively, E favors peripheral fat deposition and is critical for initiating PHV as pubertal increases in E promote increases in bone length augmenting epiphyseal mineralization in both girls and boys (18,50). Collectively, these endocrine events work in concert to partially determine peak skeletal development.

Effects of Biochemical and Hormonal Changes on Skeletal Accrual Throughout Puberty

The influences of endocrine factors on pediatric skeletal development has received insufficient attention, and there is a need to better define the role of key circulating biochemical and hormonal parameters (eg, E, T, IGF-1, sclerostin, 25-hydroxyvitamin D [25-(OH)D] parathyroid hormone [PTH], etc.) in modulating specific bone parameters. In boys, periosteal expansion (ie, larger bone size) is driven predominantly by T (but not E), and to a lesser extent increases in T are also associated with better trabecular microarchitecture (ie, higher bone volume fraction and trabecular thickness; 33). By contrast, in girls, trabecular bone microarchitecture does not appear to change significantly throughout puberty and increases in bone size are driven mainly by IGF-1, but not T or E (33). These findings are perhaps surprising given the critical roles of E in both the female (30) and male (31) adult skeleton, but may reflect local aromatization of T to E in bone.

Additional biochemical factors known to play important roles in skeletal development include sclerostin, 25-(OH)D and PTH. Sclerostin is a well characterized potent inhibitor of Wnt signaling and bone formation (3). Recently, serum sclerostin levels were shown to be negatively associated with cortical thickness and cortical volumetric bone mineral density (vBMD) in girls and positively associated with cortical porosity in both sexes (32), suggesting that changes in sclerostin production during growth may play a role in defining cortical bone structure. Further, numerous studies suggest that serum levels 25-(OH)D (vitamin D) have important effects on BMD and bone metabolism, although the prevalence of vitamin D deficiency and its potential negative consequences for skeletal accrual have not been extensively studied in youth. PTH is another important biochemical parameter that should be considered in the context of skeletal development. Interestingly, cortical thickness and cortical vBMD are inversely associated with serum PTH levels in boys during midpuberty (33; the period coinciding with PHV), which supports the hypothesis that there is an increased requirement for calcium during peak linear growth (47). This hypothesis is supported further by the apparent increase in cortical porosity at the radius during peak linear growth in both sexes (33). However, whether cortical bone deficits are more severe in boys and girls who sustain fractures as compared with nonfracture controls is an important question.

Because approximately one in three otherwise healthy children will suffer at least one fracture (38), and the distal forearm is by far the most common site afflicted during the peripubertal years (38), there is considerable interest in establishing an underlying skeletal basis for these fractures. Recent evidence suggests that boys and girls who suffered a mild trauma distal forearm fracture (DFF) had significant deficits at the distal radius in bone strength (ie, failure load) and had higher (worse) fall load-to-strength ratios, along with significant reductions in cortical thickness (14). Further, skeletal deficits in boys and girls with a mild trauma DFF were found to be generalized as evident by similar changes in bone strength at the distal tibia, as well as regional deficits in bone mass (eg, hip, spine, and total body). By contrast, both boys and girls who suffered a moderate trauma DFF had virtually identical values for all of the measured bone parameters compared with sex-matched

nonfracture controls. Because boys and girls who fracture in the setting of mild trauma likely have underlying skeletal deficits, they may benefit from exercise interventions to optimize bone strength during childhood and adolescence. Further, relatively little is known regarding the key biochemical and hormonal parameters that determine mild trauma fracture risk in youth and how these parameters change in response to exercise. Future studies are needed to address these important unresolved questions.

Influences of Soft Tissue Composition on Bone Development in Youth

Knowledge of modifiable risk factors that compromise skeletal development may permit optimization of such factors to reduce the impact of potential skeletal deficits early in life on subsequent fracture risk. While skeletal muscle mass has been consistently linked to the achievement and maintenance of bone mass and structure in youth (39,66), the relationship between fat and bone has been more controversial. Mechanistically, adipose tissue and bone are connected by multiple pathways (29), and during growth, it is certainly plausible that fat may be causally implicated in mediating changes in bone mass and/or structure to offset gains in body mass that typically accommodate increased adiposity. However, because obese children and adolescents have proportionately greater skeletal muscle mass relative to their height (40), relations between adipose tissue and the skeleton may be caused, at least in part, by bone modeling adaptations that occur in response to muscle contractions and osteogenic factors (myokines) that communicate between skeletal muscle and bone cells (6). Nevertheless, the strong relations between skeletal muscle and bone do not preclude the possibility that excess fat could also have an independent endocrine or mechanical loading effect on the skeleton, particularly at weight-bearing sites. Further, while excess adiposity appears to be an important risk factor for DFFs in pediatric populations (20,21), obesity also seems to be protective against fragility fractures at most skeletal sites later in life (10). Thus, it cannot be assumed that relationships between fat and bone do not change across different stages of the lifespan.

In addition to total fat mass, mounting evidence suggests that *pathogenic* fat depots (eg, visceral and intramuscular regions) may secrete various proinflammatory cytokines that negatively impact bone (29). Indeed, several studies have noted the opposing effects of visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) on the skeleton (19,52). Although the precise mechanism(s) for these contrasting effects remain unclear, higher SAT may benefit bone via the secretion of leptin and aromatase actions, which both have osteogenic effects, enhancing BMD and bone size (9). In contrast, increased VAT is associated with higher levels of proinflammatory cytokines (eg, TNF- α and IL-6) that may negatively affect both bone modeling and remodeling (29). In addition, effects of fat on bone likely vary by skeletal region (ie, weight-bearing versus non-weight-bearing sites). Clearly, further work is needed to better understand the key factors that mediate fat-bone crosstalk, and ultimately, the clinical implications of increased adiposity on fracture risk.

Exercise in Enhancing Skeletal Gains in Children and Adolescents

There is now overwhelming evidence that exercise can optimize skeletal development. Indeed, the prevailing dogma established over 100 years ago (67) posits that bone mass and

structure change in a predictable manner in response to mechanical strains imparted from skeletal muscle contractions and ground reaction forces. While this is not controversial, the most effective exercise prescription and how much investment in this prescription is needed to significantly impact bone health continues to be debated. These questions are not easily answered, although substantial progress has been made. Owing to the difficulties in measuring bone strain directly in humans, our knowledge of the skeleton's response to mechanical loading has largely come from animal studies in which various loading conditions can be precisely manipulated. From these studies, optimal skeletal loading regimens have been described (58). Indeed, there is a robust relationship between strain magnitudes (load) and bone's osteogenic response (49,51). Perhaps surprising, however, increasing frequency (25) and duration (61) of loading cycles is met with diminishing returns, although mechanosensitivity of bone cells can be restored with the implementation of rest periods between loading sessions (48).

Information from animal studies has been fundamental in informing the design of exercise regimens that aim to enhance human bone health throughout the lifespan, including during the critical pre- and early-pubertal years when the skeleton is highly receptive and most sensitive to exercise. The reason(s) for this window of opportunity during the pre- and early-pubertal years is not completely clear, although there are plausible biological bases for both periods being the time when the skeleton is most responsive to loading exercises; that is, exercise may enhance bone formation in a synergistic fashion in the presence of GH (prepubertal years) or lower levels of sex steroids (early pubertal years). Indeed, exercise is a potent stimulus for GH secretion. Moreover, in response to mechanical loading, some have speculated that the presence of higher levels of E (ie, late pubertal years) may favor endocortical (inner) bone apposition, as opposed to deposition of bone on periosteal (outer) surfaces (4). Since periosteal expansion is more important in establishing biomechanical bone strength (55), the pre- and early pubertal years may represent the most opportune periods for optimizing bone structure. It should be emphasized, however, that in the absence of adequate dietary energy (eg, certain eating disorders), female athletes in particular can be at high risk for developing compromised reproductive function and skeletal health (referred to the female athlete triad; 44). Therefore, proper nutrition counseling and monitoring are important considerations when children and adolescents engage in exercise.

Because the osteogenic response to exercise is unique, bone health exercise regimens tend to differ from regimens for other systems (eg, cardiovascular), although some overlap is often integrated to target a wider range of tissues, with the aim of improving multiple health outcomes simultaneously. Following findings from animals, most human skeletal exercise studies have focused on resistance training and high impact exercises (eg, jumping). Further support for these regimens comes from cross-sectional studies of athletes who regularly engage in these activities and that report almost universally that exercise-trained individuals have greater bone health than their sedentary peers (8,15,37,45). Comparisons among athletes who consistently participate in loading versus nonloading recreational activities and sports lend additional support to the potential causal role of exercise in optimizing skeletal health (8,24,28). Association, however, does not prove causation, and most cross-sectional studies of exercise and bone are limited by considerable selection bias. Thus, the optimal

exercise regimen to elicit skeletal adaptations during growth is an important question that will require additional randomized prospective controlled trials to be conclusively resolved.

Historically, most prospective bone health exercise trials have focused on slowing or reversing age-related bone loss in older women and men. However, the relatively recent recognition of the peripubertal years as a unique period when the skeleton is particularly responsive to exercise has led to a number of exercise interventions in youth. Modes of exercise have included dance, games, jumping, and resistance training, as well as various combinations of these activities. Hence, the predominant focus has been on weight-bearing loading exercises, although there is an urgent need to also incorporate exercises that target non-weight-bearing skeletal sites (ie, upper extremities). In 2007, a systematic review of 22 pediatric bone exercise studies found that over 6 months, gains in bone mass and BMD were 0.9–4.9% in prepubertal, 1.1–5.5% in early pubertal, and 0.3–1.9% in late pubertal exercisers, respectively, compared with matched controls. Many of these studies had a high risk for bias and poor exercise compliance was a common concern. Nevertheless, at the time, weight-bearing exercise appeared to optimize bone health in youth, and thus was generally advocated as an evidence-based means of enhancing peak skeletal accrual. A 2014 meta-analysis of weight-bearing pediatric exercise trials, however, concluded that exercise increases bone mass and BMD during the prepubertal years, but had little or no effect during puberty (5). This meta-analysis also found a high risk for bias and poor compliance as limitations inherent to most studies. Furthermore, it remains incompletely understood whether any exercise-induced skeletal gains during youth are maintained into later life. Therefore, it is still unclear whether pediatric bone-loading exercise prescriptions are an effective form of osteoporosis prophylaxis. To date, relatively few prospective trials have measured bone structural parameters, which can increase bone strength without concomitant changes in bone mass or BMD (54). Such trials are currently ongoing and should provide novel insights into the important unresolved question as to whether bone-loading exercise during childhood and adolescence can optimize peak bone strength.

Does Exercise When Young Provide Lifelong Benefits Toward Bone Health?

Bone-building interventions early in life are based on the underlying premise that optimizing peak bone strength in childhood and adolescence is beneficial for the prevention of osteoporosis later in life. Pediatric studies have shown that weight-bearing activity, especially high-impact exercise, promotes bone mineral accrual (5,13) and possibly structural changes, but whether such adaptations have a lasting effect and compensate for age-associated bone loss and therefore reduce osteoporotic fracture risk is not known. Prospective observational studies suggest some of the benefits of exercise on bone during youth track into young adulthood (11,12,53) and perhaps beyond (59,64), including a benefit on bone strength (65). However, prospective assessment of lifelong benefits is not feasible. Indeed, most data on this issue come from cross-sectional studies of former athletes compared with less active controls. In adults, BMD declines relatively quickly to preexercise levels upon cessation of exercise following an intervention (36), and there is no reason to believe that some regression would not occur in youth (28). Nevertheless, some

other benefits (eg, on geometry, microarchitecture, and/or strength) may persist despite loss of bone mass (64,65). Such a proposition is plausible if lasting structural adaptations occur; for example, if bone size were to increase in response to exercise. All else staying equal, bone's resistance to bending is increased as its material is distributed further away from its longitudinal axis. Studies of baseball players, soccer players, and individuals involved in racket sports consistently demonstrate skeletal hypertrophy in the active, dominant limb versus the nondominant side (4,27), with enduring advantageous bone strength adaptations (65). As noted earlier, bones may be particularly responsive during the pre- to early pubertal years (41), as retrospective analyses of former athletes have consistently shown that athletes who begin training during this period have greater adaptations than those who begin training in late puberty (4). These loading effects seem to be region and surface specific (4) corresponding with the described hormonal changes during development. Because exercise during youth preferentially deposits new bone on the outer periosteal surface to increase bone size (4,22) and bone loss during aging occurs primarily on the endocortical surface (1,56), the optimization of bone size and strength acquired through exercise during youth has the potential to continue independent of the maintenance of adaptations in bone mass.

Summary

Maximizing skeletal accrual and bone strength in children and adolescents cannot be solved safely with available drugs. Thus, nonpharmacological strategies are needed to reduce the burden of skeletal deficits and fractures in youth. Knowledge of modifiable factors that determine skeletal development may permit optimization of skeletal health during growth and could potentially offset reductions in bone strength with aging. The peripubertal years represent a unique period when the skeleton is particularly responsive to loading exercises, and there is now overwhelming evidence that exercise can optimize skeletal development. Because exercise is safe, accessible, inexpensive, and efficacious for optimizing peak skeletal accrual and bone strength in children and adolescents, it may represent the most effective strategy to reduce the population burden of skeletal deficits and fractures. However, despite considerable effort, we still do not know how much investment in exercise early in life is needed to protect against the development of osteoporosis and fractures with aging. Clearly we have much to learn, but for the time being, it seems best to encourage our children to exercise and build a healthier skeleton, even though they may potentially lose exercise-induced benefits later in life, rather than to never encourage exercise at all.

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