

## Mini-Review

# Exercise Training, Menstrual Irregularities and Bone Development in Children and Adolescents

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**Abstract.** Weight bearing physical activity plays an important role in bone development. This is particularly important in children and adolescents since bone mineral density reaches about 90% of its peak by the end of the second decade, and because about one quarter of adult bone is accumulated during the two years surrounding the peak bone growth velocity. Recent studies suggested that the exercise-induced increase in bone mineralization is maturity dependent, and that there is a “window of opportunity” and a critical period for bone response to weight bearing exercise during early puberty and premenarchal years. This supports the idea that increase in physical activity during childhood and adolescence can prevent bone disorders (like osteoporosis) later in life. In contrast, strenuous physical activity may affect the female reproductive system and lead to “athletic amenorrhea”. The prevalence of “athletic amenorrhea” is 4–20 times higher than the general population. As a consequence, bone demineralization may develop with increased risk of skeletal fragility, fractures, vertebral instability, and curvature. Menstrual abnormalities in the female athlete result from hypothalamic suppression of the spontaneous pulsatile secretion of gonadotropin releasing hormone. Recent studies suggested that reduced energy availability (increased energy expenditure with inadequate caloric intake) is the main cause of the central suppression of the hypothalamic pituitary-gonadal axis. Therefore, effort should be made to optimize the nutritional state of female athletes, and if not successful, to reduce the training load in order to prevent menstrual abnormalities, and deleterious bone effects in particular during the critical period of rapid bone growth.

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**Key Words.** Exercise—Puberty—Female—Bone—Mineralization—Amenorrhea

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## Introduction

Physical activity plays an important role in tissue anabolism, yet little is known about the mechanisms that link patterns of exercise with tissue anabolism. Considerable anabolic stimuli arise even from relatively modest physical activity of daily living. Therefore, anabolic effects of exercise training are not limited to individuals participating in competitive sports who focus particularly on improvements of muscle strength and endurance. For example, complete limb immobilization<sup>1</sup> or lack of gravitational mechanical loading (e.g. space flight<sup>2</sup>) lead to destructive bone loss, while bone formation dramatically increases when immobilized subjects resume exercise.<sup>3</sup> This has led to the popular conclusion that physical activity enhances bone formation and, consequently, bone mineral density (BMD).

The exercise-associated anabolic effects are age and maturity dependent. It is remarkable that spontaneous levels of physical activity, energy expenditure, muscle strength and bone turnover exhibit some of their most rapid increases during childhood and adolescence. The combination of rapid growth and bone development, high levels of physical activity, and spontaneous puberty-related increases in anabolic hormones (growth hormone, insulin-like growth factor-I, sex steroids and bone turnover markers) suggest the possibility of integrated mechanisms linking exercise with anabolic bone responses during this important life period.

Moreover, the potential contribution of physical activity to increase bone mass is particularly important in children and adolescents since BMD reaches about 90% of its peak by the end of the second decade,<sup>4</sup> and because about one quarter of adult bone is accumulated during the two years that surround the peak bone velocity.<sup>5</sup> This supports the idea that patterns of

physical activity during childhood and adolescence can act to prevent bone disorders (like osteoporosis) later in life.

Despite strong indirect evidence in highly trained athletes or immobilized subjects linking physical activity with increased bone formation, direct evidence for this relationship in an otherwise healthy, mobile population, is lacking. A variety of investigators have been unable to find a consistent relationship between *habitual* physical activity levels and bone mass in moderately active adults.<sup>3,6-8</sup> In contrast, the majority of cross-sectional studies in normally active children and adolescents suggest that higher levels of physical activity are indeed associated with increased bone mass.<sup>9-11</sup> Interestingly, similar to adults, there have been few controlled, prospective, longitudinal studies designed to examine the effect of a quantified training intervention on bone turnover and bone mineral density.

### Habitual Physical Activity

The relatively new development of assays for circulating biochemical markers of bone turnover<sup>12</sup> now allow us to gain greater mechanistic insight into the effects of factors like exercise and maturation on bone development. We recently reported the effect of a brief (5 weeks) randomized, prospective endurance-type training intervention on bone turnover markers in late pubertal males and females. Training was accompanied by about 15% higher total energy expenditure (by the doubly labeled water technique), and resulted in significant increases in  $\text{VO}_2$  max and thigh muscle volume (by magnetic resonance imaging) in the trained but not in the control subjects.<sup>13,14</sup> Training led to substantial increase (15–39%) in all bone formation markers (osteocalcin, bone specific alkaline phosphatase, and C-terminal propeptide of type-I collagen [PICP]) in both late pubertal males<sup>14</sup> and females<sup>13</sup> (Fig. 1), while there was no change in these markers in the control subjects. The finding of large increases in bone formation markers in the trained subjects strongly supports the hypothesis that relatively brief endurance type training in adolescent males and females specifically stimulates new bone formation independent of the ongoing puberty-associated increases in these markers. In addition it emphasizes the important role of exercise training for bone formation during periods of *rapid* bone development.

Interestingly, the highest training-associated increases in both late-pubertal males and females were in PICP. Increase in PICP indicates new formation of Type I collagen which, while abundant in bone, is not solely limited to bone.<sup>15</sup> PICP is released from skin, cartilage, tendons, and other connective tissues, suggesting, perhaps, that there is a generalized increase in

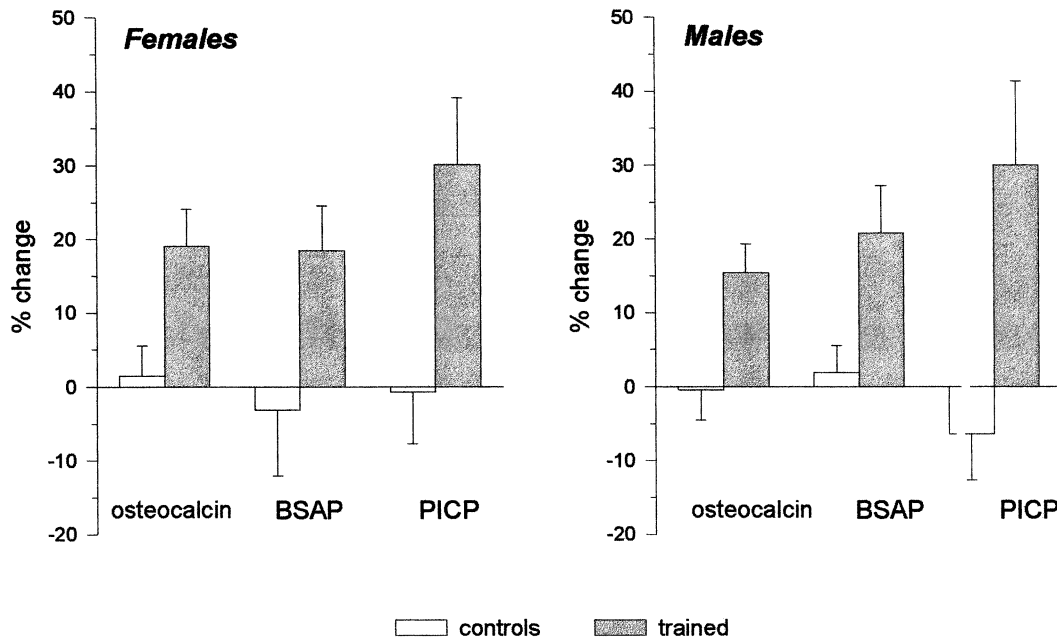
the synthesis of these tissues following endurance training in fitter adolescents.

It was suggested that changes in growth hormone (GH) and insulin-like growth factor-I (IGF-I) mediate the exercise-associated increase in bone strength. However, in the former studies in late pubertal males and females<sup>13,16</sup> despite the biochemical evidence for new bone formation, training led to an unexpected decrease in circulating IGF-I and other growth factors without any change in over-night GH secretion. This indicated that *circulating* GH and IGF-I levels were probably not responsible for the increase in bone turnover. It is possible, however, that training-associated changes in *local* bone IGF-I and/or other growth factors affected bone formation by autocrine and paracrine mechanisms.

Very few studies evaluated the effect of prolonged training periods on bone mineralization in children and adolescents. Studies in prepubertal children found that 8 months of weight bearing activity interventions resulted in greater increases (1.2–5.6%) in bone mineral content and areal BMD. Interestingly, while the training intensity in these studies varied markedly (highly intensive, repetitive box jumping<sup>17</sup> vs. 30 min, 3 times/week of mainly weight bearing games<sup>18</sup>), the impact on bone mineralization was similar. This may suggest that in prepubertal children the type or intensity of the activity is less important than the extent of increase in weight-bearing activity per se.

Recently, McKay et al<sup>19</sup> demonstrated that an easily implemented school-based jumping intervention (10 tuck jumps 3 times/week, and incorporation of jumping, hopping and skipping into twice weekly physical education classes for the whole school year) augmented BMD at the trochanteric region in prepubertal and early pubertal children. In addition, addition of a circuit training program of jumping exercise to the regular physical education classes in prepubertal and early pubertal girls resulted in greater femoral neck cross sectional area and bending strength compared to controls.<sup>20</sup> This emphasizes the important role of physical activity in *schools* for the improvement of bone strength development, and prevention of osteoporosis later in life, by reaching the majority of the children and adolescents, and by using experienced personnel, accessibility to existing facilities and an environment that is familiar to and relatively comfortable for the students.

Morris and coworkers<sup>21</sup> studied the effect of weight bearing endurance activities (30 min, 3 times/week for 10 month) on bone metabolism in early pubertal, premenarchal girls. They found a significant greater increase (up to 5.5%) in total body, lumbar, spine and proximal femur bone mineral density in girls from the intervention group compared to controls.



**Fig. 1.** The effect of a brief (5-week) endurance-type training intervention on bone formation markers in late-pubertal females (left panel) and males (right panel). Training was associated with a significant increase in all markers in both genders suggesting new bone formation.

In contrast, training interventions in postmenarchal girls using 6.5 months of hydraulic resistance training<sup>22</sup> or 9 months of high impact resistance training<sup>23</sup> (3 sessions/week in both interventions) were not associated with greater increase in bone mineral content compared to well matched controls. Moreover, Heinonen et al<sup>24</sup> showed that an intense 9 months jumping program (20 min twice a week) resulted in a significant greater increase in lumbar spine and femoral neck bone mineral density in premenarchal girls, but not in postmenarchal girls compared to age and maturity matched controls.

### The Importance of Timing of Physical Activity

Based on these observations MacKelvie et al<sup>25</sup> suggested in a recent review that exercise training-induced increase in bone mineralization and strength is maturity dependent. They hypothesized that the higher levels of factors that enhance bone formation such as estrogen, testosterone, GH, and IGF-I in premenarchal years improve the effect of exercise and mechanical loading on bone turnover and mineralization. During postmenarchal years the level of these bone enhancing factors decrease, and as a consequence the effect of weight bearing exercise interventions on bone mineralization is attenuated. They concluded that there is a “window of opportunity” and a critical period for bone response to weight bearing exercise during early puberty and premenarchal years. However, despite the greater ability of physical activity to increase bone accrual during

the growing years, it is becoming apparent that there is currently a decrease in school-based or leisure time participation in noncompetitive types of exercise experiences for children and adolescents.<sup>26</sup>

Therefore, pediatricians and other primary care physicians must take an active part in encouraging children and adolescents to increase their weight bearing activities during this critical period in order to increase peak bone mass and to prevent osteoporosis later in life. However, the optimal prescription of the type, intensity, frequency and duration of an exercise intervention for enhancement of peak bone mass in children and adolescents for the prevention of osteoporosis (or reduction of fracture risk) later in life is still unknown.

It should be emphasized that the idea that exercise and increased mechanical loading have a pivotal role in enhancement of bone development is not limited to puberty. Recent studies demonstrated that a brief (4 weeks) passive range of motion exercise with gentle compression of both the upper and lower extremities resulted in increased bone mineral density (by single and dual photon absorptiometry<sup>27,28</sup>), or in attenuation of the natural decrease in bone strength (by quantitative ultrasound measurements of bone speed of sound<sup>29</sup>) in premature infants during early postnatal months of life. Therefore, exercise may play a key role in the prevention of osteopenia of prematurity. These studies emphasize, again, the important role of exercise training for bone formation and mineralization during periods of *rapid* bone development.

## Competitive Sports

Exercise training, however, is not only associated with bone formation and increased mineralization. Strenuous physical activity may affect the female reproductive system and lead to “athletic amenorrhea.”<sup>30,31</sup> The term “athletic amenorrhea” refers to amenorrhea that cannot be explained by any known etiology other than the exercise training, and therefore its diagnosis is made by exclusion. It was shown that the prevalence of amenorrhea among athletes is 4–20 times higher than the general population,<sup>32</sup> and appears to be higher mainly in younger athletes who train intensively, and in certain types of sports in which leanness may provide a competitive advantage (e.g. long distance runners, gymnasts, etc.). One of the major concerns of athlete amenorrhea is the low estrogen levels, which despite the relative protection by the weight bearing activity, may result in reduced bone mass, due to inadequate acquisition of peak bone mass during the critical period of puberty, and/or due to excessive bone loss in later years. This osteopenia may expose the young female athlete to an increased risk of skeletal fragility, fractures, and vertebral instability and curvature.<sup>33</sup>

Menstrual abnormalities in the female athlete result from hypothalamic dysfunction, and suppression of the spontaneous pulsatile secretion of gonadotropin releasing hormone.<sup>33</sup> Several mechanisms have been suggested to explain this suppression. It was suggested that the later age of menarche in female athletes is due to genetic factors, since non-athletic mothers and sisters of female amenorrheic athletes have also higher prevalence of menstrual abnormalities.<sup>34</sup> Genetic factors, however, cannot explain such a higher prevalence (up to 20 times) above the general population.

Other studies suggested that athletic amenorrhea results from hormonal effects such as increased prolactin, endorphins, and/or androgens. However, prolactin levels are even suppressed in hypothalamic athletic amenorrhea,<sup>35</sup> and the acute prolactin response to exercise is smaller compared to eumenorrheic athletes. In addition, there is no difference in baseline androgen level between amenorrheic and regularly menstruating athletes, and the androgen response to exercise is smaller.<sup>36</sup>

It was also suggested that the psychological stress related to heavy training and competition was the cause for menstrual irregularities. No differences were found, however, in psychological tests or mood scores between amenorrheic and other athletes.<sup>36</sup>

It was hypothesized that suppression of the reproductive system in female athletes is the result of an increased physiological stress. However, it was shown that some female athletes develop menstrual irregularities while others who participate in similar,

or sometimes even identical, training intensity protocols maintain normal menstrual cycles. Recently, in a series of investigations, Loucks and colleagues suggest that reduced energy availability is the main cause of the central suppression of the hypothalamic-pituitary-gonadal axis.<sup>37</sup> They defined energy availability as dietary energy intake minus energy expenditure, and demonstrated that the relationship between energy expenditure and caloric intake and not each component separately is the major factor that alters both metabolic and reproductive hormone secretion in elite athletes. Furthermore, they showed that there is an energy availability threshold of 20–25 kcal/kg lean body mass, and that menstrual disturbances occur only in female athletes who have energy availability below this threshold.<sup>38</sup> The existence of such a threshold provide an explanation for the fact that despite training in the same group with similar training programs, some elite female athletes develop amenorrhea while others continue to menstruate regularly. It was also demonstrated that low energy availability was the cause for the reduced LH pulsatility, and the suppression of other anabolic hormone secretion such as tri-iodothyronine (T<sub>3</sub>), insulin and insulin-like growth factor-I; and that increase in caloric intake in order to compensate for the high energy expenditure was able to prevent this suppression in the elite female athlete.<sup>37</sup> This hypothesis was supported also by animal studies that showed that training-associated amenorrhea in monkeys was reversed by dietary supplementation without restriction of the training intensity or duration.<sup>39</sup>

Similar to other energy deficient states, the body conserves its energy sources to adapt to the major stress (in this case exercise training), and will not expend energy on luxury activities such as reproduction and growth. These observations suggest that athletic amenorrhea is a nutritional problem, and therefore may be prevented or reversed first by dietary reforms. Only if these nutritional changes will not result in the expected improvement in the menstrual cycle, is moderation of the exercise regimen warranted.

## Summary

Weight bearing physical activity and increased mechanical loading have beneficial effects on bone mineralization and development in children and adolescents, and in particularly during periods of rapid bone growth such as early pubertal and the premenarchal years. Since the majority of peak bone mass is accumulated by the end of the second decade, efforts should be made to emphasize the importance of regular exercise during this critical period in order to optimize bone development and prevent osteoporosis later in life. This is

particularly important in females, since recent studies indicate that they tend to decrease their habitual physical activity level during adolescence.

On the other hand, there is increased tendency for participation of children and adolescents in competitive sports in recent years. This practice, especially if associated with inadequate caloric intake, exposes the young female athletes to several health risks and hazards such as menstrual irregularities and hypoestrogenism. As a consequence, bone demineralization may develop with increased risk of skeletal fragility, fractures, and vertebral instability and curvature. Pediatricians should be aware of these potential health risks, and should make special efforts to guarantee that the present race of the young athlete for glory will not result in irreversible health damage in the future.

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