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Resistance Training and Bone Mineral Density during Growth

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Key words
- tibia
- osteocalcin
- pyridinoline
- DXA

Abstract

This study examined the efficacy of two different resistance training programs in enhancing bone modeling and bone mineral density (BMD) in maturating rats. One exercise mode involved lifting a lighter weight with more repetitions (LI), while the other regimen involved lifting a heavier weight with fewer repetitions (HI) where the total volume of work between exercise programs was equivalent by design. Twenty-three male rats were randomly divided into control (Con, n = 8), LI (n = 7), and HI (n = 8) groups. The LI and HI groups were conditioned to climb a vertical ladder with weights appended to their tail 4 days/wk for 6 wks. After training, serum osteocalcin (OC) was significantly ($p < 0.05$) higher in both HI (45.2 ± 1.7 ng/ml) and LI (39.1 ± 2.2 ng/ml) when compared to Con (29.9 ± 0.9 ng/ml). Left tibial BMD was significantly ($p < 0.05$) greater for HI (0.231 ± 0.004 g/cm^2) when compared to both LI (0.213 ± 0.003 g/cm^2) and Con (0.206 ± 0.005 g/cm^2) with no significant difference between LI and Con. The results indicate that both HI and LI are effective in elevating serum OC, implicating an osteogenic response; however, only HI resulted in a significant elevation in BMD.

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Introduction

Exercise is commonly accepted as an important factor for bone accrual during growth and attenuating bone loss during senescence. Of the two primary modes of exercise, resistance training has been recognized to be more effective in eliciting an osteogenic response when compared to endurance training [9]. Given the recognized importance of resistance training, studies to determine the most effective strength training program upon the bone during the formative years are noticeably absent. Previous observations in prepubertal boys [3] and premenarcheal girls [12] following various high-impact or strength building exercise programs have reported increases in bone mineral accrual compared with sedentary children. These initial reports [3,12] provide evidence on the importance of exercise for increasing bone mineral density (BMD) during growth. However, as with any cross-sectional comparison in children where growth is relatively rapid, matching the growth velocity between the exercise and control groups was impossible and could conceivably explain the differences observed in the exercised groups [3]. Further, while these initial reports are noteworthy, the most effective strength building exercise program to elicit an osteogenic effect during maturation remains unresolved. In this regard, the use of maturating animals would provide greater control over these confounding variables; however, identifying a strength training mode in animals to mimic resistance training in humans has been a significant obstacle.

Previous studies in rats to mimic resistance training involved electric shock as the motivation for animals to jump with weighted vests [10,13,22], simulating leg squat exercise. In a different study, Robling et al. [16] immobilized the forelimb and applied compressive force to the ulna using a motor-driven device to ensure equivalent mechanical loads between groups. However, this required the animals to be anesthetized during the loading procedure. While both these prior animal studies help to eliminate the confounding variables associated with the use of humans, they also introduce other factors such as the independent effects of electric shock upon the bone and the use of anesthetic drugs, which can negatively impact blood flow. In contrast, Notomi et al. [14] introduced a different model of resistance training for animals that involved climbing a wire meshed tower. Hornberger and Farrar [8] later verified the efficacy of a similar model (i.e., vertical ladder climbing task) for producing muscle hypertrophy that was confirmed in the Flexor Hallucis Longus. In a prior study, we also employed a modified version of this vertical ladder climbing task and found it to be an effective resistance training stimulus for rats [6].

While the maturation period has been advocated as a propitious time to implement resistance training to stimulate bone acquisition, the type of strength training program that would elicit the greatest elevation in BMD remains equivocal. Specifically, during the growth period it is unclear whether lifting heavy weights using fewer repetitions (abbreviated for this paper as high-intensity) is more effective than lifting lighter weights using more repetitions (abbreviated for this paper as low-intensity). The purpose of the current study was to determine the influences of high-intensity and low-intensity resistance training on markers of bone modeling and bone mineral density in maturating animals while maintaining the total volume of work at equivalent levels. We employed the vertical ladder climbing task in animals to help eliminate the confounding variables associated with human studies. Finally, we hypothesized that high-intensity resistance training would induce a greater elevation in bone mineral density than low-intensity resistance training.

Fig. 1 The ladder climbing apparatus. A rat is shown climbing the 1-meter, 90° incline ladder with weights appended to the tail.

Materials and Methods

Animals

The experimental protocol for this study was preapproved by the Chapman University Institutional Review Board and in accord with the Public Health Service policy on the use of animals for research. Twenty-four male Wistar rats (initially ~225 grams, ~8 weeks old) obtained from Charles River Laboratories (Wilmington, MA, USA) were housed individually and maintained on a reverse 12/12 hour light/dark cycle. The animals were acclimated to their living conditions for 1 week with food and water provided *ad libitum*. Then they were randomly assigned to either a control group (Con, n = 8), a resistance trained group where the animals lifted a low amount of weight with high repetitions (LI, n = 8), or another resistance trained group where the animals lifted a high amount of weight with fewer repetitions (HI, n = 8).

Resistance training

The strength training regimen consisted of a vertical ladder-climbing task in which weights were appended to the rat's tail (**Fig. 1**). There were 26 rungs across the 1-meter ladder, with the animals positioned to help ensure that they performed each sequential step. Thus, one repetition along the length of the ladder required 26 total lifts by the animal (or 13 lifts per limb). These resistance trained animals were operantly conditioned to climb the ladder in order to avoid a vat of cold (room temperature) water beneath them. The exercised animals trained 4 days/week for a total of 6 weeks. The control animals were handled on the same days as the trained groups in order to equalize any stress attributable to handling. All animals were weighed at the beginning of the week to monitor weight gains and, for the resistance trained animals, to help determine the amount of weight to append to their tails for the remainder of the week. The LI animals started with 5% of their body weight (BW) appended to their tail, and each week the resistance was increased by 5% BW until they were carrying 25% of their body weight by the beginning of week 5, where they maintained this resistance until the end of week 6. The HI animals started with 30% of their body weight appended to their tail, and each week the resistance was elevated by 30% BW until they were carrying 150% of their body weight by the beginning of week 5, where they similarly maintained this resistance until the end of week 6. The number of ladder climbs (i.e., total repetitions) for the LI group was twofold higher than the HI group. The resistance (% body weight appended to their tail plus their body weight) and the number of repetitions served to equate the total volume of work between HI and LI groups throughout the 6-week training period. It should be noted that one of the animals in the LI group refused to climb the ladder at the beginning of the second week. This animal was eliminated from the LI group which accounts for the decrease in sample size for LI (n = 7).

Experimental protocol

To minimize any residual effects of the last bout of exercise, animals were sacrificed 48 hours after the last training session. To help substantiate a resistance training effect, and consistent with Hornberger and Farrar [8], the Flexor Hallucis Longus (FHL) was rapidly dissected from the right hindlimb, weighed, and immediately frozen in liquid nitrogen for the subsequent determination of protein content. The left hindlimb was rapidly amputated, positioned, and frozen in liquid nitrogen for the assessment of bone mineral density of the tibia. Finally, blood samples were collected, placed on ice, allowed to clot, centrifuged, and the serum was frozen for the subsequent measurement of osteocalcin and pyridinoline cross-links. All tissue and serum samples were kept at – 80 °C until its analyses.

Table 1 Animal weight and protein content in FHL

Group	Initial BW (grams)	Final BW (grams)	FHL weight (grams)	Total FHL protein (mg/muscle)
Con	252.3 ± 2.1	442.0 ± 9.5	245 ± 14	55.76 ± 3.20
LI	251.2 ± 3.3	448.5 ± 3.8	277 ± 6	61.16 ± 1.89
HI	258.5 ± 2.4	402.7 ± 4.4#	286 ± 11*	65.86 ± 2.19*

Con = control group (n = 8), LI = low intensity resistance training group (n = 7), and HI = high intensity resistance training group (n = 8). Where BW = body weight and FHL = Flexor Hallucis Longus. # Significant difference between HI vs. all other groups. * Significant difference between HI vs. Con

Chemical analyses

A protein assay [11] was used to determine the protein concentration in the FHL as an indirect indicator of training (i.e., muscle hypertrophy). A sandwich ELISA (rat osteocalcin kit from Biomedical Technologies, Inc., Stoughton, MA, USA) was employed to determine serum osteocalcin levels (an indicator of osteoblast activity). The intra-assay variation was < 4% and the inter-assay variation was < 7%. Serum pyridinoline cross-links (an indirect indicator of osteoclast activity) were measured using a competitive enzyme immunoassay (PYD EIA kit from Quidel Corp., San Diego, CA, USA). The intra-assay variation was < 6% and the inter-assay variation was < 8%. A microplate reader (MaxLine, Molecular Devices Corp., Sunnyvale, CA, USA) was used with the absorbance set at 450 nM for the ELISA or 405 nM for the EIA. Finally, a Dual Energy X-ray Absorptiometer (DXA – GE Lunar Prodigy, Chicago, IL, USA, USA) employing the small animal software module (version 6.81) was used to assess the BMD of the left tibia. The frozen left hindlimb was positioned and the tibia was scanned. Three consecutive measurements were performed with repositioning between each scan. The average was used as the BMD and the coefficient of variation for repeated scans was < 1.4% for each group.

Calculations and statistics

Total protein in the FHL was calculated as the product of protein concentration and muscle mass. Work (i.e., training volume) was determined as the product of the total weight lifted by the animal (body weight plus the amount of weight appended to the tail), the acceleration due to gravity, and the distance covered. The total training volume for LI and HI was expressed in Joules. For total training volume, a Student's *t*-test was used to determine statistical significance. For all other comparisons, an ANOVA was employed, and when a significant F ratio was identified, a Tukey's post hoc test was used. The level of significance set was at $p < 0.05$ for all statistical comparisons and the results are expressed as the mean ± standard error (SE).

Results

The initial body weight was not significantly different between groups; however, after the 6 week resistance training program, the body weight for the HI group was significantly lower than the other groups (**Table 1**). While the body weight was lower for HI, the total training volume was not significantly different between HI vs. LI (**Fig. 2**). Further, while the total protein content in the FHL demonstrated a trend toward an increase in LI when compared to Con ($p = 0.28$), only the HI group had significantly higher protein content than the control group (**Table 1**). Serum pyridinoline (PYD) cross-links did not significantly differ between the Con (2.28 ± 0.10 nmol/L), LI (2.27 ± 0.09 nmol/L), and HI (2.79 ± 0.32 nmol/L) groups. In contrast, serum osteocalcin levels (OC) demonstrated significant elevations with increasing training intensities (**Fig. 3**). The bone mineral density from the left tibia from the HI group was significantly greater than Con (**Fig. 4**). In contrast, the BMD from LI was not significantly different from Con ($p = 0.32$).

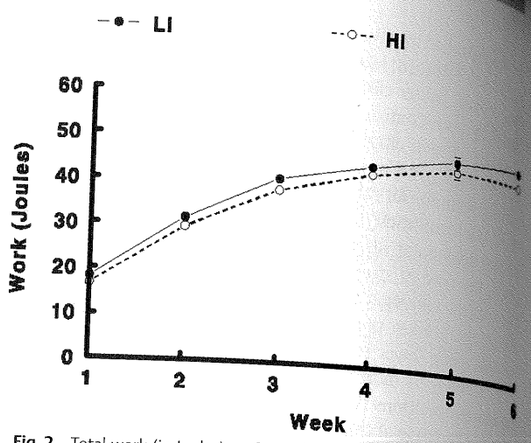

Fig. 2 Total work (in Joules) performed for each training day during the week for the low-intensity resistance trained group (LI, n = 7) and the high-intensity resistance trained group (HI, n = 8). No significant difference between groups.

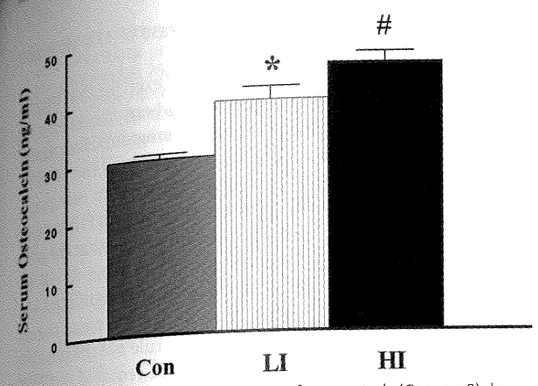

Fig. 3 Serum osteocalcin concentrations from controls (Con, n = 8), low-intensity resistance training group (LI, n = 7), and high-intensity resistance training group (HI, n = 8). *Significant difference between LI vs. Con. # Significant difference between HI vs. all other groups.

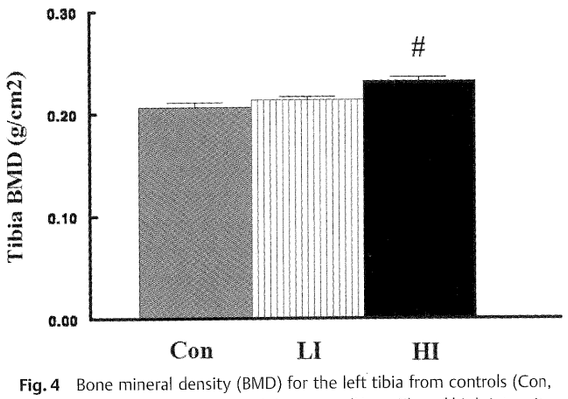

Fig. 4 Bone mineral density (BMD) for the left tibia from controls (Con, n = 8), low-intensity resistance training group (LI, n = 7), and high-intensity resistance training group (HI, n = 8). # Significant difference between HI vs. all other groups.

Discussion

The current study demonstrated that a high-intensity resistance training regimen effectively induced both hypertrophy in the FHL and a concomitant osteogenic response in maturating rats, as supported by elevations in serum osteocalcin and an increase in tibial BMD. In contrast, the low-intensity resistance training regimen resulted in a propensity toward hypertrophy in the FHL. Further, there was evidence of an osteogenic response as indicated by the significant elevation in serum osteocalcin albeit in the absence of any increase in tibial BMD. These differences were evident even though the total volume of work was kept constant between HI and LI training groups. Thus, our 6-week strength training program in maturating rats suggests that lifting heavy weights with fewer repetitions was effective for eliciting an osteogenic response whereas lifting lighter weights with more repetitions may require additional time to evoke the elevation in BMD.

Due to the challenge of getting animals to lift a heavy mass, studies employing a strength training model for use in animals are limited. Previous studies in rats used an electrical stimulus or unconscious animals [10,16,17,22] where either could inadvertently impose other confounding variables. Notomi et al. [14] were among the first investigators to introduce and report a modified resistance training exercise protocol in animals for the study of bone modeling. Maturating male rats, initially 10 weeks of age, voluntarily climbed a wire meshed tower for 8 weeks [14]. The resistance training effect from tower climbing resulted in significant increases in BMD in the midfemur and proximal tibia compared to sedentary controls [14]. Given the success of a climbing protocol in animals to mimic resistance exercise, we modified the training program of Hornberger and Farrar [8] and used a vertical (90°) ladder climbing task in the absence of electric shock. In contrast, we used water to motivate animals to climb as we are unaware of any studies that might suggest an alteration in BMD with occasional water immersion. It should be noted that after the first few weeks our animals were not consistently exposed to the water, as most climbed without motivation. On occasion, we used a squirt bottle where the stream was directed beneath them and the noise prompted the animals to continue the climb. Similar to Hornberger and Farrar [8] we used the total protein content in the FHL as an indirect indicator of skeletal muscle hypertrophy to support the adaptations associated with our resistance training program. Since the site of bone deposition is specific to the mechanical loads placed upon it [21], we chose to examine the tibial BMD in accord with the location of the FHL.

Using a serum biochemical marker of an osteogenic response, HI had elevated osteocalcin levels and corresponding increases in tibial BMD. While the serum osteocalcin levels were also augmented in the LI group, there was no significant enhancement in either total protein in the FHL or tibial BMD. As such, our results suggest that muscle hypertrophy may not be required for elevated indices of bone formation such as serum osteocalcin. In support, neural adaptations (e.g., improved synchronization of motor units) could also elicit strength gains in the absence of muscle hypertrophy [18] and still provide the requisite stimulus for bone modeling. Thus, while the increase in FHL muscle protein and concomitant elevations in serum osteocalcin and tibial BMD, observed from only the HI group, suggest that 6 weeks was appropriate, we recognize that more time (i.e., more than 6 weeks of training) might be required to eventually observe the increase in BMD for the LI group.

An elevation in BMD resulting from exercise in maturating rats is not a novel observation. Previous reports in maturating animals have demonstrated the effectiveness of exercise in promoting an osteogenic response [7,9,13,14,23]. However, the novelty of the current study is the type of resistance exercise that appears to be more effective in eliciting the modeling response. In humans, this has been difficult to elucidate. While high-impact exercise in humans tends to be more effective in eliciting bone formation than low-impact exercise [1,5,20], ostensibly the enhancement of bone mass could be attributable to differences in the amount of work performed between the different exercise intensities. In human studies where the volume of work was kept constant, the results were equivocal. In older women, there was no elevation in BMD following either a high-intensity or low-intensity resistance training program where the volume of work was equivalent between exercise programs [15]. In contrast, in young women performing high- vs. low-intensity eccentric resistance training, where the volume of work was similarly kept constant between exercise programs, an elevation in BMD was only observed in the low-intensity group [19]. We speculate that the discrepancy between these human studies in women could be attributable to differences pertaining to the length of training, oral contraceptive use, and/or menopausal status.

While our use of animals helps to eliminate these confounding variables, we interpret our results with caution. Bennell et al. [2] failed to observe an increase in BMD after 10 weeks of resistance training where their rats similarly engaged in a climbing task with carrying loads of 150% BW. We suspect that the different outcome in our study may be related to training volume and training days per week. The training volume for our animals was approximately 2-fold greater compared to Bennell et al. [2]. Further, our animals trained 4 days/week whereas Bennell et al. [2] trained their animals 3 days/week. While we can only speculate on the discrepancy between the currents results and Bennell et al. [2], we note that several studies support our outcome. Notomi et al. [14] observed elevations in BMD after 8 weeks of daily tower climbing in maturating female rats where the animals covered distances of over 135 meters per day. Further, Westerlind et al. [22] demonstrated increases in rat cancellous bone area after 6 weeks of resistance training in mature rats. Thus, the increase in BMD elicited by our high-intensity resistance training program was in accord with most of the prior studies involving strength training.

Although our result demonstrating an increase in BMD was consistent with prior reports, the mechanism for bone deposition appears to be capricious. Yeh et al. [23] examined the impact of

a 6-week exercise (treadmill) program and determined that the training-induced bone modeling in their maturating female rats was the result of a decrease in bone resorption. In contrast, we failed to observe a decline in osteoclast activity as indicated by serum pyridinoline cross-links. In fact, our results suggest that the increase in BMD in male rats is attributable to an elevation in osteoblast activity as indicated by the elevation in serum osteocalcin. As such, the significant increase in BMD for the HI group appears to be the result of more bone deposition rather than a decline in bone resorption. The discrepancy suggests either sex differences in the bone modeling response to exercise, the type of exercise employed (i.e., treadmill vs. ladder climbing), or the potential for oscillatory effects between bone resorption and bone deposition. Despite the mechanistic discrepancies between animal studies, our results support the few prospective studies in prepubertal boys [3] and premenarcheal girls [12] that high-intensity, strength training is an effective means for eliciting a bone modeling response. Further, given the equivalent training duration, training frequency, and volume of work between HI and LI, we conclude that training intensity is an essential factor for this type of exercise contributing to the elevation in BMD in our maturating animals. The significant difference in carrying weight between HI (i.e., 150% of BW) and LI groups (i.e., 25% of BW) support greater loads upon the skeleton for the HI animals. Whether this will similarly apply to maturating humans remains to be determined and should be examined with caution. However, it offers a potential insight into the type of training program that would optimize bone accrual during growth.

Finally, we recognize several limitations of our study. First, while numerous reports have employed the DXA in animals [2, 7, 9, 13, 14], there are limitations associated with using a DXA for the determination of BMD. Specifically, bone mineral density, as determined by the DXA is expressed as an area (i.e., g/cm^2) and may not account for changes in bone size where increases in height could contribute to elevations in BMD [4]. While we recognize the limitations associated with the DXA, we also note that it was sensitive enough to detect the alterations in BMD despite differences in body weight between groups. In support, the HI group had the lowest body weight, ostensibly implicating a lower bone size, yet they also had the greatest BMD. Further confirmation of an osteogenic response in the HI group was the serum biochemical markers. However, as it pertains to the serum markers for bone formation and bone resorption as well as BMD, we note that these parameters were measured at a single time point. Measuring markers for bone formation, bone resorption, and BMD over the course of the training program would provide additional information leading to a more conclusive explanation of our findings. Third, we examined the scan on the whole tibia without regard to regions (i.e., metaphyses and cortical shaft) performed only at the end of the training period. Thus, it is unknown if the training effect occurred primarily in the mixed bone and/or the cortical bone and whether there are oscillatory changes in BMD throughout the training period. Fourth, given that serum biochemical markers of bone formation are precursors to changes in BMD, we note that more time might be necessary before skeletal changes could be detected from the LI group. In partial support, given the existing data trends, it would require an additional 22 animals to attain statistical significance in the BMD for the LI group where the relative increase in BMD compared to controls would be 2.5%. Alternatively, if more time was allowed, we may have observed that the BMD from LI could approach the relative increase of 11% we report for the HI group compared to controls.

In summary, using animals and a mode of exercise that mimics human progressive resistance training where the volume of work was equivalent between HI and LI programs, we provide evidence that high-intensity resistance training is the most effective stimulus to elicit an osteogenic response in maturating rats. This is supported by concomitant elevations in FHL protein, serum osteocalcin levels, and tibial BMD. We note that the positive adaptations in both skeletal muscle and bone for HI occurred within our 6-week time frame. Given the significant elevation in serum osteocalcin from LI as well as the trend toward an augmentation in FHL protein, we cannot rule out the possibility that more time (i.e., > 6 weeks) might be required to finally observe the increase in skeletal muscle hypertrophy and BMD as a result of the LI resistance training program.

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