Cancellous bone adaptation to tibial compression is not sex dependent in growing mice

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Abstract

The skeleton has the intrinsic ability to sense and respond to its mechanical environment, and this adaptive ability is most pronounced at young ages (21, 24). Strategies designed to increase bone mass and alter architecture before the attainment of peak mass may be the most effective at reducing fracture risk when bone loss occurs (3, 7, 22, 39). Exercise studies in young adults suggest sexual dimorphism exists in the response to mechanical loading, but few comparisons have been made between female and male cohorts (1, 9, 19, 36). Differentiating sex-specific responses will enable mechanical loading strategies to be developed to maximize bone growth in both sexes.

Whether sex-specific factors affect the skeletal response to loading is unclear (9, 18, 19, 30, 36, 45). Male tennis players have larger upper extremities, in both dominant and non-dominant arms, than females (9, 19). Similarly, after resistive training, males had greater spinal and femoral mineral density (36). However, extremely small sample sizes and short experimental duration limited the power of these studies and confounded interpretation. Additionally, the skeletons of male rodents, but not of females, were responsive to treadmill running (18, 45). However, the mechanical environment induced in the skeleton during these activities was unknown. When similar in vivo loads were applied in rats, the cortical tissue of both sexes responded similarly to ulnar compression (30). To date, no study has examined the effect of sex on the anabolic response to controlled in vivo loading in the cancellous compartment of mice.

The mechanical environment in the skeleton is difficult to characterize during exercise studies; thus the characteristics of mechanical loading critical to anabolic bone adaptation have been examined by applying controlled in vivo loads in animal models. Functional adaptation has primarily been studied in the diaphyses of mammalian long bones (16, 27, 34, 41, 42); however, most clinical skeletal fractures occur at sites with large volumes of cancellous bone, such as the hip, the spine, and the distal radius. Noninvasive compression has been used to apply physiological loads to the mouse tibia allowing the adaptive response of both cancellous and cortical sites to be investigated. In vivo tibial compression increased bone formation and mineral content in the metaphyses of healthy growing mice (8, 12, 29, 38), prevented bone loss due to hormone deficiency in growing male mice (11), and enhanced the effect of parathyroid hormone treatment in adult female mice (38). Based on these studies, applied mechanical loads can be used to increase peak bone mass in the cancellous compartment in young subjects.

In this study, we applied in vivo tibial compression to growing, young adult male and female mice to determine if cancellous adaptation is sex dependent during skeletal growth. We applied peak loads that engendered similar physiological diaphyseal and metaphyseal strains in both sexes (17, 26, 31, 35). Bone mass, architecture, and dynamic formation in the proximal metaphysis in response to dynamic mechanical loading were compared between males and females via microcomputed tomography and histomorphometry. The mechanical environment in the proximal metaphysis during loading was characterized using finite element analysis.

MATERIALS AND METHODS

Animals. Nine-week-old male and female C57Bl/6 mice (Jackson Labs) were acclimatized in our facility for 1 wk. Mice were housed by sex in groups of four to five with ad libitum access to food and water. Body masses were recorded daily and used to monitor the health of...
the mice over the course of the experiment. At the start of the experiment, male and female mice weighed 22.3 ± 1.3 and 16.9 ± 0.8 g, respectively. All experimental procedures were approved by Cornell University’s Institutional Animal Care and Use Committee.

In vivo load-strain calibration. The relationship between applied compression and bone tissue deformation for the left tibia was established for 10-wk-old mice in vivo (n = 5/sex). This relationship was used to determine the applied load that engendered +1,200 με at the medial midshaft of the tibia (8, 12). This strain magnitude corresponded to peak strain values in the rat ulna during unrestricted running (31) and typical peak strain values in a number of vertebrates during normal locomotion (2, 27, 33). Single element strain gauges (EA-06-015LA-120, Micromeasurements) were prepared (2, 17, 31) and attached to the medial surface of the tibial midshaft aligned with the bone’s long axis. While mice were anesthetized, a range of dynamic compressive loads (peak loads ranging from −2 to −25 N) were applied, and strain measurements recorded simultaneously (National Instruments, Labview v8.2). No tibia failures occurred within this load range. The slopes of the strain-load regressions were determined to be +0.0150 N/με (95% confidence interval (CI): −0.006, −0.020) for female mice and −0.0084 N/με (95% CI: −0.003, −0.014) for male mice and were not significantly different from each other by t-test. Therefore, we chose the lower of the two regression slopes (male), which required approximately −11 N to induce +1,200 με.

Mechanical loading. The mice (n = 14/sex) underwent dynamic compression of the left tibia 5 days/wk for 10 days over 2 wk using a custom-made tibial loading device (11, 12). One-thousand two hundred loading cycles were applied at 4 Hz (11, 12) with −11.5 ± 0.3 N peak load (corresponding to approximately +1,300 με) and a constant −2.3 ± 0.3 N during the dwell period (12). The loading device was modified from our previous design (11, 12) to implement feedback control of the applied loads (National Instruments, Labview v8.2) using an in-line force transducer (ELFS-T3E-20L, Measurement Specialties). The right tibia served as the contralateral control. During all loading sessions, the mice were under isoflurane anesthesia (2% Isoflurane, 1.0 l/min, Webster). Normal cage activity was allowed between loading sessions.

Intraperitoneal injections of calcine (20 mg/kg, Sigma Aldrich) and demeclocycline (20 mg/kg, Sigma Aldrich) were administered 4 and 14 days before euthanasia, respectively. Mice were euthanized by CO2 inhalation 2 wk after loading commenced. Tibias were dissected free of soft tissue and fixed in 10% neutral buffered formalin for 48 h, then stored in 70% ethanol.

Micro-computed tomography. All pairs of tibias were scanned using quantitative micro-computed tomography (MS-8 MicroCT, GE Healthcare Systems) (12). Isotropic voxel resolution was 15 μm. A global threshold of 1,100 HU (0.27 g/ml) was used to segment mineralized tissue from water and soft tissue. For each tibia, a uniform volume of interest (VOI) including both cancellous and cortical bone, and cortical VOIs (right) included only the cortical shell. MicroCT VOIs (Fig. 1A) were used to generate corticocancellous and cortical models. The FE VOIs included 5% of total tibial length and were centered within the VOI (dashed box). Corticocancellous VOIs (left) included both cancellous and cortical bone, and cortical VOIs (right) included only the cortical shell.

Fig. 1. A: representative cancellous volume of interest (VOI) used for micro-computed tomography (microCT) analysis. Each cancellous VOI was defined in the proximal end of the tibia and excluded the cortical shell. The proximal end of the VOI began below the primary spongiosa and extended distally 10% of total tibial length. B: representative VOIs used for finite element (FE) analysis. Each VOI was 5% of total tibial length and was centered within the VOI used for microCT analysis (dashed box). Corticocancellous VOIs (left) included both cancellous and cortical bone, and cortical VOIs (right) included only the cortical shell.

scans were coarsened (following a convergence study) by combining 2 × 2 × 2 voxels to yield a single voxel with side length 0.03 mm, and coarsened voxels were converted into eight-noded linear brick elements (~54K elements per model). Elements were assigned isotropic material properties with a uniform modulus of 20 GPa and a Poisson’s ratio of 0.3 (Abaqus v6.7, Dassault Systèmes Simulia) (44). Nodes at the distal surface of the model were restricted to in-plane motion and prevented from rigid-body motion. Strains were determined at the element centroids.

To characterize the tissue strain environment during the loading experiment, a uniform displacement was applied to the proximal surface of the models that resulted in an 11.5 N compressive reaction force at the distal surface. Elements were identified in the control corticocancellous models that coincided with the cancellous VOIs used for the microCT analysis (see Micro-computed tomography). In these elements, the longitudinal strains (εzl) were determined. We assumed that strains in the control limbs under simulated loading conditions were representative of the strains induced at the onset of the experiment. In females, a uniform −0.09% apparent strain applied at the proximal surface resulted in −11.5 N reaction force at the distal surface. The cancellous tissue strains ranged from −2,437 ± 155 με to +455 ± 221 με (average Min to Max). In males, a uniform −0.07% apparent strain resulted in −11.5 N reaction force at the distal surface and the cancellous tissue strains ranging from −2,134 ± 430 με to +286 ± 94 με. The maximum and minimum strain values did not differ statistically between the sexes by linear mixed model. Metaphyseal cancellous tissue experienced primarily compressive longitudinal strains during in vivo applied loading. The mean tissue strains were 19% lower (p = 0.003) in males (−341 ± 31 με) vs. females (−421 ± 31 με).
To characterize the effects of adaptation on the apparent stiffness of the proximal metaphysis, the reaction force (N) was calculated for a uniform strain of \(-0.1\%\) applied to the proximal surface of all models. The proportion of the load transmitted through the cancellous tissue was determined from the ratio of the cortical to corticocancellous reaction forces, an indicator of load sharing between the metaphyseal cortex and cancellous tissue.

Histomorphometry. Histomorphometric analyses were performed on the proximal tibiae for a subset of mice (\(n = 5/sex\)) using methods detailed elsewhere (28). Briefly, after fixation the bones were stained en bloc with Villanueva Mineralized Bone Stain (Arizona Histology and Histomorphometry Services) for 5 days, dehydrated with ethylene glycol monoethyl ether, cleared in methyl salicylate, and then embedded in methyl methacrylate. Undecalcified 7-\(\mu\)m-thick frontal sections were cut using a rotary microtome (Leica 2265, Nussloch) equipped with a tungsten carbide knife. Sections were cover-slipped and used for fluorescence microscopy analysis of bone resorption and formation. Sections were analyzed using an OsteoMeasure system (Osteometrics) connected to a microscope (Zeiss Axioskop, Carl Zeiss). All measurements were made by a single observer who was blinded to the specimen identity.

Measurements within the cancellous compartment and the endosteal and periosteal cortical surfaces of the proximal metaphysis were performed on a 1-mm-wide \(\times\) 2.5-mm-long region beginning 0.5 mm below the growth plate. Bone resorption was assessed from eroded surface (ES/BS = eroded surface/bone surface measured as eroded perimeter (EPm)/bone perimeter (BPm), %); bone formation was assessed from the mineralizing (fluorochrome labeled) surface (LS/BS labeled surface/BS measured as = dLS + 0.5 sLS from single and double LS, %), mineral apposition rate (MAR, \(\mu\)m/day) and surface-based bone formation rate (BFR = mineralizing surface \(\times\) MAR/BPm, \(\mu\)m/yr).

Statistical analysis. The effects of sex and loading on the adaptive response to tibial loading and change in body mass were determined with a linear mixed model with repeated measures (JMP v7.0, SAS Institute). The within-subject factor was limb, loaded (L) or control (C), and the between-subject factor was sex. Statistical significance was set at \(\alpha \leq 0.05\). All results presented are significant unless otherwise stated. If no significant interaction was present, then only main effects are reported. Percentage differences were calculated for the effects of loading [(loaded − control) \(\times\) 100/control] and sex [(males − females) \(\times\) 100/females]. All values are represented as means \(\pm\) SD.

RESULTS

Effect of loading. Two weeks of in vivo tibial compression significantly increased cancellous bone mass in both sexes (Fig. 2). Cancellous BV/TV increased 73\% in the loaded tibias relative to control tibias (Fig. 3). Increases in bone mass corresponded to changes in cancellous architecture and tissue properties (Fig. 3). Mean Tb.Th increased (+75\%) while Tb.Sp decreased (−19\%). Increased tBMD (+18\%) contributed to greater bone mass in the loaded tibias following 2 wk of compression. Loading did not affect tibial length.

Increased cellular activity contributed to increases in cancellous bone mass (Table 1). Bone formation was enhanced with loading in the cancellous envelope. In purely cancellous surfaces, LS/BS increased 22\%, which corresponded to higher MAR (+97\%) and BFR (+137\%), in loaded limbs relative to control limbs. Bone resorption was also enhanced with loading in cancellous bone. At the periosteal and endosteal cortical...
Adaptation in cancellous tissue mass and architecture resulted in stiffer proximal metaphyses in the loaded limbs. For the 0.01% deformation applied in the FE analysis, the reaction force in the loaded limbs was greater than in the control limbs (L: 27.0 ± 1.8 N vs. C: 14.4 ± 2.7 N). In loaded limbs, a greater proportion of load was carried by cancellous rather than cortical tissue, as reflected by 10% decreased cortical to cancellous load ratio (L: 0.55 vs. C: 0.61 ± 0.07).

**Effect of sex on the response to loading.** For all measurements, the differences between loaded vs. control limbs were similar between male and female mice. Male mice had more cancellous tissue (+53% BV/TV) due to greater Tb.Th (+9.1%) and tBMD (+2.9%), and smaller Tb.Sp (−36%) compared with females (Fig. 3). As a result, metaphyseal tissue was stiffer in males, as reflected by 14% greater corticocancellous compressive reaction force (males: 22 ± 6.6 N vs. females: 19 ± 7.1 N) and a 16% lower cortical to corticocancellous load ratio (males: 0.53 ± 0.05 vs. females: 0.63 ± 0.05). Cellular activity did not differ by sex.

Over the 2-wk experimental period, males and females continued to grow as indicated by increased body mass. Body mass increased similarly in males and females (+2.7%), to 22.9 ± 1.2 g in males and to 17.4 ± 0.9 g in females. Males were 32% heavier and had 4% longer tibias than females (males: 17.1 ± 0.2 mm vs. females 16.4 ± 0.2 mm).

**DISCUSSION**

Tibial compression increased cancellous bone mass and altered architecture similarly in growing adult male and female mice. The increases in cancellous bone mass seen in experimentally loaded tibias were produced by dramatic increases (2- to 3-fold) in bone formation rates compared with control limbs. As a result, the stiffness of cancellous tissue increased with adaptation, and more load was transmitted through cancellous than cortical tissue in loaded than in control limbs.

The effects of sex on cortical adaptation to increasing mechanical loading have been variable. In growing and mature rodents, females showed no response to treadmill running while males increased geometric measures in the diaphyses (18, 45). Mechanical parameters such as applied load and strain magnitude are seldom measured in exercise studies; thus the results cannot be related directly to the mechanical environment experienced by the skeleton. A strength of our model is that well-defined, controlled physiological loads are delivered to the tibia. In an analogous model delivering compression to the rat ulna, the relative cortical response was similar in males and females despite greater absolute deposition rates in males (30), a finding similar to our morphometric results in cancellous bone. Furthermore, the peak applied loads in the rat were chosen to produce matching peak strains at the midshaft in each sex, a methodology identical to ours. Our focus, however, was on the response of cancellous bone to loading within a physiological range of strains measured in cortical bone (17, 27, 31). Mechanical strains can be measured in vivo only on bone surfaces, which limited our measurements to cortical sites. We chose the mid-diaphysis because functional strain...
levels at this site are conserved across a range of animals and are well documented. These opposing results with sex across studies may reflect fundamental differences in adaptation between controlled in vivo loading and exercise. Because the adaptive changes to loading in male and female limbs were nearly identical in the present study, detecting a significant number of animals (e.g., >600 animals with 90% confidence for BV/TV measurements, based on post hoc power analysis).

Based on body size alone, greater strains at the medial diaphysis would be expected in female mice than in male mice for similar applied loads. Female mice are smaller than age-matched male mice as indicated by body mass (13, 37), femoral and tibial cross-sectional area (5, 10, 32, 37), and tibial length and moment of inertia (37). Female mice also have lower vertebral and distal femoral bone volume fraction and trabecular thickness than age-matched males (13). However, the strain-load relationship from in vivo strain-gauging established that similar loads were required to engender target strain levels in males and females. Cortical material property differences may compensate for the geometric effects. Conflicting data exist on sex-specific material properties or composition of mouse bone tissue (18, 37). We did not observe any differences associated with sex in tissue mineral density, suggesting other factors not examined in this study may contribute to whole bone mechanical behavior.

Because the strain environment within the proximal tibia during loading cannot be determined in vivo, specimen-specific FE models of proximal metaphyses were used to simulate tibial compression and quantify cancellous strains and changes in stiffness. FE models based on microCT image data have become a common technique for estimating the mechanical environment of cancellous bone (20, 44), and this approach has been shown to replicate experimental data (4). In vivo loading was simulated by applying a uniform displacement to the proximal metaphysis producing a compressive reaction force of 11.5 N. The applied displacement required to achieve the −11.5 N reaction force in the corticocancellous models differed between males and females, reflecting that male control tibias had greater cancellous mass and thicker trabeculae in the proximal metaphysis. However, the resulting peak cancellous strain values did not differ by sex, as they did for our cortical strain measurements, verifying that we were inducing similar strain environments in the proximal metaphysis in males and females. These results were influenced by using partial models, applying homogenous moduli to both new and existing bone, and using an applied displacement boundary condition.

Few in vivo models are available to study the response of cancellous bone to mechanical loading. Previous models have induced an adaptive response in cancellous compartments (14, 15, 43) but required invasive surgery, which can confound interpretations of the response to loading due to associated healing processes. Also, nonphysiological loading regimes were often employed (6, 23). Our model addresses several of these limitations. Compression of the tibia is noninvasive, and adaptation is present when the applied loads are physiological in magnitude and direction. Our approach has the potential to address the effects of numerous variables, such as age and genetic factors, on the mechanisms modulating cancellous bone adaptation. Tibial compression may alter the soft tissues in the knee joint, but the present study focused on bony adaptation.

Our results in female mice are more pronounced than other tibial loading studies that applied similar load levels. A different load-strain dose response was observed in this study relative to previous studies in our laboratory. Previously, growing (10 wk) male C57Bl/6 mice increased BV/TV by only 13% after 2 wk of loading at −3 N with no significant changes in trabecular thickness or separation (12). The osteogenic response of male mice in the present study was greater (Fig. 3), likely due to the higher peak load magnitude used here (−11.5 N). The greater load was chosen based on in vivo strain calibration, which resulted in a different strain-load relationship than was established previously. Because the tibia is a highly curved bone, small variations in gauge position can produce significant changes in strain readings. In the present study, bone strains were measured over a smaller area due to smaller strain gauges, which are more accurate, and may explain our lower strain readings. Discrepancies with other studies (8, 29, 38) are likely attributable to different loading parameters, including the number of applied cycles, frequency, and duration of pauses. In these other tibial compression studies, a 10-s rest was inserted between each loading cycle (8, 29, 38) and far fewer total loading cycles were applied per session than in our study (40 vs. 1,200). In addition, these prior studies the animals were loaded only 3 times/wk compared with 5 times/wk in our study. Combined, the total time

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**Table 1. Dynamic histomorphometry for the proximal metaphysis of male and female mice after 2 wk of in vivo tibial compression**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sex</th>
<th>Loaded (Left)</th>
<th>Control (Right)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancellous surface</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ES/BS</td>
<td>Female</td>
<td>15 ± 7.1</td>
<td>13 ± 3.0</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>16 ± 5.0</td>
<td>18 ± 5.0</td>
</tr>
<tr>
<td>LS/BS</td>
<td>Female</td>
<td>23 ± 2.7*</td>
<td>20 ± 4.2</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>20 ± 4.5*</td>
<td>16 ± 3.8</td>
</tr>
<tr>
<td>MAR, μm/day</td>
<td>Female</td>
<td>1.9 ± 0.48*</td>
<td>0.66 ± 0.86</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>1.7 ± 0.40*</td>
<td>1.1 ± 0.72</td>
</tr>
<tr>
<td>BFR, %/yr</td>
<td>Female</td>
<td>160 ± 49*</td>
<td>55 ± 79</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>123 ± 23*</td>
<td>61 ± 42</td>
</tr>
<tr>
<td>Proximal metaphyseal perioseal surface ES/BS</td>
<td>Female</td>
<td>0.49 ± 0.30*</td>
<td>0.64 ± 0.30</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>0.33 ± 0.17*</td>
<td>0.82 ± 0.20</td>
</tr>
<tr>
<td>LS/BS</td>
<td>Female</td>
<td>0.04 ± 0.06</td>
<td>0.00 ± 0.00</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>0.04 ± 0.11</td>
<td>0.06 ± 0.14</td>
</tr>
<tr>
<td>MAR, μm/day</td>
<td>Female</td>
<td>0.53 ± 0.82</td>
<td>0.00 ± 0.00</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>0.55 ± 1.4</td>
<td>0.27 ± 0.66</td>
</tr>
<tr>
<td>BFR, %/yr</td>
<td>Female</td>
<td>0.22 ± 0.37</td>
<td>0.00 ± 0.00</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>0.54 ± 1.3</td>
<td>0.33 ± 0.81</td>
</tr>
<tr>
<td>Proximal metaphyseal endosteal surface ES/BS</td>
<td>Female</td>
<td>0.17 ± 0.19*</td>
<td>0.03 ± 0.04</td>
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<tr>
<td></td>
<td>Male</td>
<td>0.15 ± 0.09*</td>
<td>0.04 ± 0.05</td>
</tr>
<tr>
<td>LS/BS</td>
<td>Female</td>
<td>0.77 ± 0.10</td>
<td>0.81 ± 0.10</td>
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<tr>
<td></td>
<td>Male</td>
<td>0.82 ± 0.10</td>
<td>0.70 ± 0.15</td>
</tr>
<tr>
<td>MAR, μm/day</td>
<td>Female</td>
<td>2.5 ± 0.63</td>
<td>2.4 ± 0.40</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>2.0 ± 0.45</td>
<td>2.7 ± 0.71</td>
</tr>
<tr>
<td>BFR, %/yr</td>
<td>Female</td>
<td>7.2 ± 2.3</td>
<td>7.1 ± 1.32</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>6.1 ± 1.4</td>
<td>7.1 ± 2.70</td>
</tr>
</tbody>
</table>

Data are represented as means ± SD. ES/BS, eroded surface; LS/BS, mineralizing surface; MAR, mineral apposition rate; BFR, bone formation rate.

*Loading, p < 0.05 by linear mixed model with repeated measures.
the skeleton was experiencing loads was much less compared with our protocol (120 cycles/wk vs. 6,000 cycles/wk) and likely contributed to our enhanced osteogenic response.

Gains in cancellous mass due to loading were achieved through increased cellular activity. In the cancellous envelope, both MAR and BFR increased after 2 wk in the loaded limbs relative to control limbs. In a similar study with male mice, MAR increased at a similar rate, but BFR decreased after 6 wk of tibial compression (11). The longer time period in that study may have allowed cells to reach a steady state response while bone formation may have still been in a transient phase in our study (25). In addition, osteoclastic activity was enhanced at the endosteal surface of the proximal metaphysis, further suggesting that adaptation is ongoing in our study. Increased osteoclastic activity at the endosteum and reduced activity at the periosteum may reflect an effort to increase the overall size of the cancellous envelope at the expense of the cortex, thereby increasing load transfer through cancellous bone. A similar cortical-cancellous relationship is evident when vertebrae from C57Bl/6 mice were compared with other genetic strains (40). Taken together with our FE-based stiffness, increased mechanical loading of corticocancellous sites amplifies load transfer through the cancellous envelope.

In summary, through noninvasive and well-defined mechanical loading, substantial increases in bone mass were observed in the cancellous bone of growing male and female mice. Whether these gains would be maintained after cessation of loading, and for how long, remains to be determined. Peak applied loads corresponded to similar peak strains at the tibial midshaft and in the cancellous tissue of the proximal metaphysis. Our tibial loading regime elicited enhanced adaptation in the cancellous compartment compared with previous in vivo loading studies, likely due to differences in loading parameters. In the future, additional variables such as estrogen status and age need to be investigated to understand their role in bone functional adaptation. To address bone loss and osteoporosis, the ability of mechanical loading to increase bone mass or attenuate bone loss in osteopenic subjects will need to be investigated to understand their role in bone.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

REFERENCES


