Modulation of Bone Mass and Turnover in Growing Rats by Voluntary Weight-Bearing Exercise and Glucose Supplementation

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Summary Female Sprague-Dawley rats, 9 weeks of age, were assigned to four groups: Group 0 (n=8) was dissected for base-line control, and the other three groups were fed for 3 mo: Group 1 (n=9), sedentary controls; Group 2 (n=6), running rats housed in a cage with a treadmill and pair-fed with Group 1; and Group 3 (n=7), running rats, pair-fed and allowed free access to additional glucose. The distances of voluntary running did not significantly differ between Groups 2 and 3. Menstrual cycles in these rats were apparently maintained as observed from daily running distances. The amount of glucose taken by rats in Group 3 was 3.5±0.4 (mean and SE) g/d. Body weight (BW) at the end of the experiment for Groups 1, 2, and 3 were 295.0±7.9, 211.7±5.4 (p<0.001 vs. Group 1), and 259.0±3.5g (p<0.01 vs. Group 2), respectively. The parameters of bone mass such as ash weights of the femur and bone mineral content of the lumbar spine and the tibia in Groups 1 and 2 did not differ, but the values were significantly greater in Group 3 than in Group 2. However, these parameter values corrected for BW were significantly greater in Group 2 than in Group 1 and did not significantly differ between Groups 2 and 3. The parameters of bone formation, such as serum bone alkaline phosphatase activity levels and trabecular bone formation rates corrected for BW, were significantly greater in Group 2 than in Group 1 but did not differ between Groups 2 and 3. However, the parameters of bone resorption, such as serum tartrate resistant acid-phosphatase levels, were significantly less in Group 3 than in Group 2. These results suggest that voluntary running augments the age-dependent increase in bone mass by modulating the bone turnover when an adequate energy source is supplied under conditions of normal menstruation, and an adequate supply of energy could be necessary to enhance the age-dependent increase in bone mass.

Key Words running, glucose, BMD, histomorphometry, bone marker
It has been demonstrated that physical activity increases bone mass in both the young (1, 2) and the elderly (3, 4). However, the benefit of exercise on bone may depend on several factors, such as the type of exercise undertaken (5, 6), estrogen levels in females (7, 8) and calcium metabolism (9-11). Factors of food intake, such as the amount of calcium and the number of calories ingested, seem to be important for regulating bone metabolism during exercise. Voluntary running increases the calcium use in rats (10). Vigorous weight-bearing exercise increases the dermal calcium excretion and does not increase the bone mass without adequate calcium supply (11). Physical exercise increases energy consumption, leading to a decrease in body weight if additional calories are not supplied during the exercise. Since the effect of the exercise on bone depends on the load on the skeleton, changes in body weight during weight-bearing exercise may modulate the effects on bone and turnover (12-14). The effect of reduced body weight gain because of exercise seems to be critical in adolescence, when bone mass and body weight increase rapidly (15, 16).

Against this background, we performed experiments using rats that underwent voluntary running exercise for 3 mo. To discriminate the effects of the weight-bearing exercise and calorie intake, we compared pair-fed running rats with and without glucose supplementation, measuring the parameters of bone mass, bone markers, and the trabecular bone histomorphometry. We evaluated the menstrual condition based on the distances run daily.

**MATERIALS AND METHODS**

**Experimental design**

Grouping: Thirty female Sprague-Dawley rats, 8 weeks of age, were purchased (Japan SLC, Hamamatsu, Japan) and acclimated for 10 d. They were randomly divided into four groups based on body weight: Group 0 (n=8) was sacrificed at the start of the experimental period for the base-line control. Then the other three groups were used in a 92-d experiment: Group 1 was nonexercise control rats (n=9) that were allowed free access to food (F-2 diet, solid type, Funabashi, containing 1.2% calcium and 0.96% phosphorus: Table 1) and water; Group 2 was rats (n=6) that underwent voluntary running exercise, given a similar amount of food as that for Group 1 rats (pair feeding); and Group 3 was rats (n=7) that also underwent voluntary running exercise and were given the pair-feeding diet, but allowed to take glucose freely (powder type) as an additional energy source. Each rat in the running groups was kept in a separate treadmill cage (27 × 35 × 35 cm) with a counter. The circumference of each treadmill wheel was 1 m, and the rats were allowed to run voluntarily. The temperature was kept at 23±1°C, the humidity was maintained at 50±5%, and the illuminating light remained constant for all groups from 7 a.m. to 7 p.m.

Serum and bone sampling: All rats (n=30) were injected with oxytetracycline (20 mg/kg of BW, injection) 9 and 4 d before dissection. At the end of the experiment,
the rats were weighed. They were then deprived of food overnight and anesthetized with ether, and blood samples were taken from the abdominal aorta. All the serum samples were stored at $-90^\circ C$. Bone samples, including samples of the lumbar spine, the tibiae, the femora, and the humeri, were isolated after killing by exsanguination. After the adhering connective tissues were trimmed, the lumbar spine and the tibia samples were fixed with 70% ethanol. The middiaphyseal portion of the right humerus was prepared by cutting both ends and cleaning off the bone marrow with 0.9% NaCl; then it was frozen and stored at $-90^\circ C$.

**Bone mineral density (BMD) and content (BMC) measurements.** BMD values for the L4-L5 lumbar spine and the right tibia were determined by the DXA (Hologic's QDR-1500, Waltham, USA). For each rat, measurements were performed under general anesthesia at the start of the experiment and days 30, 60, and 90 into it. The radiation beams were exposed anteroposteriorly for the lumbar spine and laterally for the tibia. The ultrahigh resolution scan mode (rat mode, Version 4.59 software, Waltham) was used. The BMD values were obtained for the lumbar spine; the proximal one third of the tibia, including the epimetaphyseal region; and the distal two thirds of the tibia, representing the cortical diaphyseal region. The coefficient of variation of the rat phantom BMD measurement was 0.91% using the ultrahigh resolution scan mode. At the end of the experiment, bone samples were taken and all the connective tissues carefully removed. The BMC values for the extracted bone samples were then measured by directly applying radiation beams.

**Bone length, ash weight, and calcium and phosphorus contents of the femur.** After the measurement of the length of the femur with a micrometer, the samples were dried at 95°C for 24 h and burnt to ash at 550–600°C for 24 h. The dry and ash weights were measured, and after the samples were dissolved in 1 N nitric acid, the calcium and phosphorus contents were determined. The calcium was measured...
by atomic absorption spectrophotometry (Shimadzu AA-640-12, Kyoto, Japan) and the phosphorus by the method of Fiske-SubbaRow (17).

Alkaline phosphatase and tartrate-resistant acid phosphatase activities and total protein levels of the humerus. The middiaphyseal portion of the right humerus was mechanically crushed and homogenized in Tris-buffered saline (TBS; 10 mmol/L Tris-HCl, pH 7.4, containing 0.9% NaCl and 1% Triton X-100) with a Polytron homogenizer (Kinematic, Luzernerstrasse, Switzerland). The homogenate was centrifuged at 10,000 rpm for 5 min, and the supernatant was used to measure the alkaline phosphatase (ALP) and the tartrate-resistant acid phosphatase (TRAP) activities; the total protein level was then determined. The ALP activity was measured by using the substrate of p-nitrophenylphosphate (18). The tartrate-resistant acid phosphatase (TRAP) activity was measured at pH 5.5. The total protein levels were determined by the biuret method (19).

Serum levels of calcium, phosphorus, bone-specific ALP, TRAP, and total protein. Serum calcium and phosphorus levels were determined by the methods described above (17). The bone-specific ALP activity was assayed by measuring the heat labile ALP activity, using a preparation of the serum treated at 56°C for 10 min before mixing with the substrate (p-nitrophenylphosphate) (18). The TRAP activity was measured at pH 5.5. The total protein levels were determined by the biuret method (19).

Histomorphometry. The proximal tibia specimens were embedded in methyl methacrylate after Villanueva’s staining. Frontal sections 15 μm thick were cut with a Reichert-Jung microtome (Model 2050 Supercut, Heidelberg, Germany) and used to observe fluorescent labels. The following dynamic bone histomorphometric parameters were measured in the secondary spongiosa and calculated as described previously (20): double-labeled surface (dLS/BS, %), mineral apposition rate (MAR, μm/d), and bone formation rate (BFR/BS, μm/%). These parameters were defined according to the nomenclature proposed by the American Society for Bone and Mineral Research (21). The area measured was the cancellous bone region approximately 0.5 mm distal from the growth plate and 0.1 mm from the endocortical surface.

Statistics. All data are expressed as means ± SE. Student’s t-tests were used to analyze the differences between the groups after an F-test. The data values in Group 2 were compared with the values in Group 1. The values in Group 3 were compared with those in Group 2. The ANOVA test (scheffe test) was also used to analyze the differences among the three groups. The differences between Groups 1 and 2, 2 and 3, and 1 and 3 were shown. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Running distance, glucose intake, and body weight

The daily running distances for Groups 2 and 3, 12,423.3 ± 1,015.0 and

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Table 2. Body weights and food intake of rats.

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2 Running + pair feeding</th>
<th>Group 3 Running, pair feeding, glucose intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial body weight (g)</td>
<td>193.6 ± 3.5</td>
<td>193.1 ± 3.5</td>
<td>193.3 ± 3.3</td>
</tr>
<tr>
<td>Final body weight (g)</td>
<td>295.0 ± 7.9</td>
<td>211.7 ± 5.4***</td>
<td>259.0 ± 3.5***</td>
</tr>
<tr>
<td>Body weight gain (g/d)</td>
<td>1.17 ± 0.06</td>
<td>0.33 ± 0.05***</td>
<td>0.82 ± 0.07***</td>
</tr>
<tr>
<td>Food intake (g/d)</td>
<td>14.2 ± 0.4</td>
<td>14.2 ± 0.1</td>
<td>14.2 ± 0.3 (17.7 ± 0.6)***</td>
</tr>
</tbody>
</table>

Values are means ± SE.
*** Significant difference from Group 1, p < 0.001 by Student’s t-test.
** Significant difference from Group 2, p < 0.001 by Student’s t-test.
★ ★ ★ Significant differences among the 3 groups p < 0.01 or p < 0.001 by ANOVA test.

The data in parentheses for the food intake of the running group (pair feeding and glucose intake) represent the total value of pair-fed diet and glucose intakes.

12,657.5 ± 2,028.9 m/d, respectively, were not significantly different. All the rats in Groups 2 and 3 had a peculiar rhythm for daily running distance, indicating a normal menstruation cycle. Although the daily food intake did not differ among groups, the additional intake of glucose in the Group 3 rats was 3.5 ± 0.4 g/d (Table 2). Body weight gain and the final body weight in Group 2 were significantly reduced compared with Group 1 (Table 2). These values in Group 3 were significantly greater than those in Group 2.

Serum levels of calcium, phosphorus, bone specific ALP, TRAP, and total protein

Serum calcium or phosphorus levels did not differ among groups (Table 3). The total protein values were significantly less in Group 2 than in Group 1. The values in Group 3, however, were significantly greater than those in Group 2. Serum glucose levels in Group 2 were significantly greater than those in Group 1, and the values did not differ between Group 3 and Group 2. Serum bone specific ALP (bALP) activity levels were significantly greater in Group 2 than in Group 1, but the difference between Groups 2 and 3 was not significant. Serum TRAP activity was significantly greater in Group 2 than in Group 1, and the values in Group 3 were less than those in Group 2.
Table 3. Levels of calcium, phosphorus, total protein, and bone markers in rat serum.

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2 Running + pair feeding</th>
<th>Group 3 Running, pair feeding, glucose intake</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Calcium (mg/dL)</td>
<td>Phosphorus (mg/dL)</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>9.69±0.14</td>
<td>4.27±0.39</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>9.62±0.16</td>
<td>4.67±0.20</td>
</tr>
<tr>
<td>**</td>
<td>7</td>
<td>9.92±0.17</td>
<td>5.23±0.23</td>
</tr>
</tbody>
</table>

Values are means±SE.

* *, *** Significant difference from Group 1, p<0.05 or p<0.001 by Student’s t-test.

†, ‡‡ Significantly different from Group 2, p<0.05 or p<0.001 by Student’s t-test.

*, ** Significant differences among the 3 groups p<0.05 or p<0.01 by ANOVA test.

bAlp, bone alkaline phosphatase activity; TRAP, tartrate-resistant acid phosphatase activity.

Size and contents of ash, calcium, and phosphorus for the femur, and levels of total protein and activities of ALP and TRAP for the humerus

Length of the femur was significantly greater in Group 3 than in Group 2 (Table 4). The values of ash, calcium, and phosphorus contents were significantly greater in Group 1 and Group 3 than in Group 2. However, when these parameters were corrected for body weight, the values in Group 3 did not significantly differ from those in Group 2.

No difference was found in the total-protein levels of the humerus among the three groups. However, the ALP activity was significantly lower in Group 2 than in Group 1, and it was greater in Group 3 than in Group 2. The TRAP activity tended to be higher in Group 2 than in Group 1, and it was significantly less in Group 3 than in Group 2.

BMD and BMC values of the lumbar spine and tibia

The BMD values in Group 2 did not significantly differ from the values in Group 1 in the lumbar spine, the proximal tibia, or the tibial diaphysis (Fig. 1-A, B, C). However, the BMD values in Group 3 were significantly greater than the...
Table 4. Bone size, bone ash, and bone minerals in rat femur.

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2 Running + pair feeding</th>
<th>Group 3 Running, pair feeding, glucose intake</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>9</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Length (cm)</td>
<td>3.53±0.02</td>
<td>3.48±0.02</td>
<td>3.60±0.02###</td>
</tr>
<tr>
<td>Ash weight (g)</td>
<td>0.70±0.01</td>
<td>0.66±0.01*</td>
<td>0.76±0.02###</td>
</tr>
<tr>
<td>Calcium (mg)</td>
<td>284.7±4.8</td>
<td>265.2±6.5*</td>
<td>298.2±9.3#</td>
</tr>
<tr>
<td>Phosphorus (mg)</td>
<td>139.4±1.9</td>
<td>121.4±3.6***</td>
<td>139.5±3.4#</td>
</tr>
<tr>
<td>Corrected ash weight (g/100 g bw)</td>
<td>0.24±0.01</td>
<td>0.31±0.01***</td>
<td>0.29±0.01</td>
</tr>
<tr>
<td>Corrected calcium (mg/100 g bw)</td>
<td>96.8±1.7</td>
<td>125.8±5.0***</td>
<td>116.2±3.2</td>
</tr>
<tr>
<td>Corrected phosphorus (mg/100 g bw)</td>
<td>47.4±1.0</td>
<td>57.6±2.3***</td>
<td>54.5±1.2</td>
</tr>
<tr>
<td>Total protein (mg/g)</td>
<td>5.15±0.35</td>
<td>5.09±0.44</td>
<td>5.04±0.16</td>
</tr>
<tr>
<td>Alp (U/g)</td>
<td>1.56±0.11</td>
<td>1.00±0.16**</td>
<td>2.11±0.08##</td>
</tr>
<tr>
<td>TRAP (mU/g)</td>
<td>56.6±5.9</td>
<td>63.6±5.0</td>
<td>42.8±1.3##</td>
</tr>
</tbody>
</table>

Values are means ± SE.

* Significant difference from Group 1, p<0.05 or p<0.001 by Student’s t-test.
# Significant difference from Group 2, p<0.05, p<0.01, or p<0.001 by Student’s t-test.
### Significant differences among the 3 groups, p<0.05, p<0.01, or p<0.001 by ANOVA test.

Alp, alkaline phosphatase activity; TRAP, tartrate-resistant acid phosphatase activity.

Values in Group 2 at the end of the experiment.

BMC values of the lumbar spine and the whole tibia in Group 2 did not differ from those in Group 1 (Table 5). The values in Group 3 were significantly greater than the values in Group 2. The BMC values corrected for body weight in Group 2 were significantly greater than those in Group 1. The corrected BMC values in Group 3 did not significantly differ from the values in Group 2.
Histomorphometry

The trabecular bone volume (BV/TV) values in the proximal tibial metaphysis did not significantly differ among Groups 1–3 (Table 6). Neither did the parameters of the mineral apposition rate (MAR), the double-labeled surface (dLS/BS), and the trabecular bone formation rate (BFR/BS). However, the BV/TV and BFR/BS values corrected for body weight in Group 2 were significantly greater than the values in Group 1, but the corrected values in Group 3 did not significantly differ from those in Group 2.

DISCUSSION

This study clearly demonstrated that voluntary running accelerated the
Table 5. Bone mineral content of the lumbar spine and the tibia of rats at the end of the experiment.

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (Control)</th>
<th>Group 2 (Running + pair feeding)</th>
<th>Group 3 (Running, pair feeding, glucose intake)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumbar spine (mg/cm²)</td>
<td>284.1 ± 6.81</td>
<td>268.1 ± 6.96</td>
<td>310.3 ± 8.50**</td>
</tr>
<tr>
<td>Tibial proximal metaphysis (mg/cm²)</td>
<td>129.1 ± 2.94</td>
<td>129.3 ± 2.92</td>
<td>150.4 ± 4.13**</td>
</tr>
<tr>
<td>Tibial diaphysis (mg/cm²)</td>
<td>116.8 ± 2.89</td>
<td>125.6 ± 2.12</td>
<td>139.7 ± 3.32**</td>
</tr>
<tr>
<td>Whole tibia (mg/cm²)</td>
<td>359.7 ± 6.80</td>
<td>380.6 ± 8.49</td>
<td>417.2 ± 8.90**</td>
</tr>
<tr>
<td>Lumbar spine corrected (mg/cm²/bw)</td>
<td>101.1 ± 2.48</td>
<td>130.0 ± 3.56***</td>
<td>126.1 ± 3.79</td>
</tr>
<tr>
<td>Tibial proximal metaphysis corrected (mg/cm²/bw)</td>
<td>46.1 ± 1.61</td>
<td>62.9 ± 26.1***</td>
<td>61.1 ± 1.94</td>
</tr>
<tr>
<td>Tibial diaphysis corrected (mg/cm²/bw)</td>
<td>41.5 ± 8.44</td>
<td>61.1 ± 1.61***</td>
<td>56.8 ± 1.46</td>
</tr>
<tr>
<td>Whole tibia corrected (mg/cm²/bw)</td>
<td>128.1 ± 3.06</td>
<td>185.2 ± 7.55***</td>
<td>169.5 ± 4.40</td>
</tr>
</tbody>
</table>

Values are means ± SE.

** Significant difference from Group 1, p < 0.001 by Student’s t-test.

** Significant difference from Group 2, p < 0.05 or p < 0.01 by Student’s t-test.

*, **, *** Significant differences among the 3 groups p < 0.05, p < 0.01, or p < 0.001, by ANOVA test.

Age-dependent increase in bone mass by glucose supplementation in growing rats. When the glucose was not given, the exercise did not increase the parameters of bone mass. However, the bone mass values corrected for body weight were significantly increased by the voluntary weight-bearing exercise, and the glucose supplementation did not further increase the corrected bone mass values compared with the running rats not given glucose.

The voluntary exercise obviously increased the energy consumption and caused catabolic effects in the rats. The body weight gain was significantly reduced by exercise. Although fasting serum glucose level was elevated, the serum total protein
Table 6. Results of the bone histomorphometry of the proximal tibia of rats.

<table>
<thead>
<tr>
<th></th>
<th>Base line</th>
<th>Group 1 Running + pair feeding</th>
<th>Group 2 Running, pair feeding, glucose intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone volume BV/TV (%)</td>
<td>54.7±3.3</td>
<td>37.3±2.1</td>
<td>38.0±1.4</td>
</tr>
<tr>
<td>MAR (μm/d)</td>
<td>3.0±0.2</td>
<td>1.9±0.2</td>
<td>2.1±0.4</td>
</tr>
<tr>
<td>DLS/BS (%)</td>
<td>21.6±2.3</td>
<td>10.5±1.8</td>
<td>14.9±2.5</td>
</tr>
<tr>
<td>Bone formation rate</td>
<td>9.4±1.2</td>
<td>3.4±0.5</td>
<td>5.4±1.3</td>
</tr>
<tr>
<td>Correlated bone volume</td>
<td>28.3±1.8</td>
<td>13.4±0.9</td>
<td>18.5±1.0**</td>
</tr>
<tr>
<td>BV/TV (%/100 g bw)</td>
<td>48.7±6.0</td>
<td>12.7±2.5</td>
<td>25.7±6.2*</td>
</tr>
<tr>
<td>Corrected bone formation rate</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are means±SE.
* Significant difference from Group 1, p<0.05 or p<0.001 by Student’s t-test.
** Significant differences among the 3 groups, p<0.05 or p<0.01 by ANOVA test.

concentration was significantly reduced in the exercise group. Although we did not obtain data of lean body mass, these data are compatible with the reduction in the fat content in the body composition of the running rats (22). The parameters of bone mass did not apparently increase, but the parameters normalized for body weight were increased significantly. Mechanical stress—not only weight-bearing exercise, but also body weight—affects positively on bone metabolism positively, and appendicular bones, such as tibiae and femora, are weight-bearing bones. Therefore to clarify the effect of exercise, the parameters might be normalized for body weight. Furthermore mechanical stress from muscles also affect bone metabolism. Thus the voluntary running exercise regimen seems to be effective in increasing the weight of the skeleton relative to whole body weight by reducing body fat.

The glucose supplementation given to running rats apparently also increased the body weight and bone mass. Since similar serum glucose levels were maintained in the rats that underwent the exercise without supplementation, the amounts of glucose voluntarily taken seemed to be within the range of glucose tolerance in the rats. Serum total protein levels were not decreased. Thus one may assume that glucose supplementation supported the development of the body weight in the growing rats. Since the parameters of bone mass were also increased, glucose appeared also to support the age-dependent increase in the bone mass. The parameters of bone mass normalized for body weight did not differ from those of

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the running rats not given glucose. Therefore the bone mass increase by glucose supplement seemed to be closely associated with an increase in body weight.

That bone formation was increased by running was indicated by the increases in the serum bALP levels, the ALP levels in bone, and the trabecular bone formation rates. Since the serum TRAP levels, another parameter of systemic bone turnover (23), were also increased, running seems to have also increased the bone mass by stimulating bone turnover. The increase in the apparent bone mass in the running rats given glucose seems to be due to the reduced bone resorption. Although the serum TRAP may not directly reflect the bone resorption in rats (23), reduced TRAP levels in the humerus by glucose supplementation is compatible with reduced bone resorption. It has been reported that bone resorption at the organ level measured by calcium kinetics was significantly decreased by increased body weight in growing rats (24), and that increased mechanical loading alleviated the decrease in the trabecular bone volume by reducing the trabecular bone resorption (25). These findings and our results suggest that bone resorption may be reduced in the glucose-supplemented rats.

There were some reports that female athletes have a lower BMD compared with age-matched nonathlete subjects (26, 27). It has been also reported that heavy exercise and dieting reduce the age-dependent increases in BMD in female adolescence (26, 27). A disturbed estrogen secretion has been suggested to affect skeletal development in females during adolescence (28, 29). In this experiment, the rats in Groups 2 and 3 were judged to have a normal menstruation cycle based on the rhythm of daily running. The estrogen condition did not seem to be disturbed by the voluntarily running regimen for either Group 2 or 3. Thus the reduction in the age-dependent increase in bone mass in the rats of Group 2 compared with those in Group 3 could be due to an insufficient intake of energy for running exercise. The maintenance of the age-dependent increase in body weight by an adequate energy supply and normal menstruation seems to be important for the normal development of the skeleton in female adolescent runners.

In conclusion, this study confirmed that running increases the bone mass relative to body weight by increasing bone turnover in growing rats, but the age-dependent increase in bone mass was not attained without glucose supplement. Although the exact mechanisms involved are not known, the supplementation of glucose during exercise serves to modulate the effects of weight-bearing exercise on bone cells and bone mass during adolescence. Running exercise increased the bone formation with or without energy supply. However, the maintenance of age-dependent body weight increase by energy supplementation during exercise is suggested to increase the bone mass by reducing the bone resorption.

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