Liver-derived IGF-I regulates cortical bone mass but is dispensable for the osteogenic response to mechanical loading in female mice

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MECHANICAL STRAIN IS THE MAJOR FEEDBACK SYSTEM regulating bone mass. The strain-driven feedback system senses the incident mechanical strain within the loaded bones. This results in formation of bone at sites subjected to increased loading to provide each bone with a mechanically appropriate size, shape, and architecture (2, 38).

In humans, the concentration of insulin-like growth factor-I (IGF-I) in serum is decreased in patients with osteoporosis (42), and low serum levels of IGF-I are associated with high fracture risk in postmenopausal women (3) and in elderly men (19). In experimental models, IGFS are the most abundant growth factors produced by bone cells and stored in bone matrix (20). IGF-I promotes bone formation (16), and its expression is upregulated in bone cells in response to mechanical loading (8, 20). Finally, conditional disruption of local IGF-I in osteoblasts (9) or osteocytes (12) resulted in loss of the bone anabolic effect of mechanical loading (9, 12).

The major part of serum IGF-I is liver derived (20, 23, 43). In addition to regulation by growth hormone (GH) (20), serum IGF-I levels are also affected by food intake, exercise, and age (20). A mouse model with liver-specific, inducible inactivation of the IGF-I gene, using the Cre-LoxP conditional knockout system, has been developed (LI-IGF-I−/− mice) (20, 23). The selective inactivation of the IGF-I gene in the liver results in an ~70–80% reduction in serum IGF-I concentration, whereas the expression of IGF-I is unaffected in other tissues, including bone (20, 23). GH secretion is increased in LI-IGF-I−/− mice secondary to decreased negative feedback by serum IGF-I (23, 40). The LI-IGF-I−/− mice have increased peripheral vascular resistance (36) and insulin resistance (25) but still a moderate elongation of lifespan (31).

Mice with deficiency of liver-derived IGF-I have no major disturbance of postnatal longitudinal bone growth or trabecular bone properties (20, 24, 44). However, cortical bone mass is clearly decreased, which is due mainly to reduced subperiosseal bone expansion, resulting in fragile bones with reduced resistance to bending (20, 24, 44). The extent to which the endocrine liver-derived IGF-I is of importance for the bone anabolic effect of mechanical loading is unknown. The present study assessed the role of liver-derived IGF-I for the osteogenic response to mechanical strain in young adult and aged mice.

MATERIALS AND METHODS

Animals and serum IGF-I. The LI-IGF-I−/− mice were generated as described previously (C57BL/6 background) (20, 23). Mice homozygous for LoxP (14) and hemizygous for Mx-Cre (10) received three intraperitoneal injections of polyinosinic-polycytidylic acid (PiPc; 6.25 μg/g body wt; Sigma-Aldrich, Stockholm, Sweden) to induce expression of the Cre protein, thereby inactivating the IGF-I gene in the liver (10). The induction of the Cre protein was performed at 1 mo of age in female mice aged 6 mo at the loading experiments or at 12 mo of age in female mice aged 19 mo at the loading experiments. PiPc-treated female littermates that were homozygous for LoxP but lacking Mx-Cre were used as controls. Previous studies have not indicated that the introduction of Mx-Cre in mice or the PiPc injections used to induce the expression of the Cre protein affect bone growth or skeletal parameters (20, 23, 24). Seven days after the PiPc injections, serum was obtained and assayed for IGF-I by a double-antibody IGF-binding protein-blocked RIA (Mediagnost, Tübingen,
Germany). The mice were housed in a standard animal facility under controlled temperature (22°C) and photo periods (12 h of light, 12 h of dark) with free access to water and food pellets (B&K Universal, Sollentuna, Sweden). Animal care was in accordance with institutional guidelines. The ethics committee at the University of Gothenburg approved this study.

**Study design.** At 6 (control, n = 11; LI-IGF-I−/−, n = 9) or 19 (control, n = 8; LI-IGF-I−/−, n = 7) mo of age, the right tibia was subjected to short periods of axial cyclic compressive loading three times/wk for 2 wk. High-resolution microcomputed tomography (µCT), followed by three-point bending, was used to assess the osteogenic response of the loaded (right) vs. the nonloaded (left) tibiae.

**Mechanical strain measurement during dynamic axial loading.** The magnitude of longitudinal mechanical strain applied to the tibia during loading was established ex vivo in a subsample of female mice (6-mo-old LI-IGF-I−/− and control mice: n = 5 and n = 4, respectively; 19-mo-old LI-IGF-I−/− and control mice: n = 3 and n = 2, respectively). The ex vivo measurements were performed in postmortem intact mice, with the tibiae still attached to the body of the animals. In each mouse, a single element strain gauge (EA-06-015DJ-120; Vishay Measurement Group) was bonded with cyanoacrylate adhesive in longitudinal alignment to the medial aspect of the tibia at 37% of its length from the proximal end. Previous studies have shown that this region corresponds to the site of greatest osteogenic response to similar loading (28). Strains were measured across a range of peak compressive loads applied with a ramped trapezoidal waveform using a 3100 ElectroForce Test Instrument (Bose, Eden Prairie, MN) with the same holding cups that were later used for in vivo loading. When the compressive force is applied to the tibia, the bone bends in the medial-lateral direction, resulting in tension on the medial surface and compression on the lateral surface (35). From the ex vivo data, a peak load [in Newtons (N)] corresponding to 3,500 ± 150 µε at the gauge site was used for the 19-mo-old mice and 2,800 ± 500 µε at the gauge site was used for the 6-mo-old mice in the in vivo loading experiments. A higher strain at the gauge site was used in 19-mo-old mice based on previous findings that, if a similar strain is applied, mechanical loading will produce a lower osteogenic response in older female mice compared with younger female mice (15). Therefore, we used a higher strain at the gauge site in the 19-mo-old mice to have comparable osteogenic responses to mechanical loading in both age groups of mice. Linear regression analysis allowed calculation of peak loads, as given in Fig. 1. Based on the ex vivo measurements, the peak loads in the in vivo loading experiments were 11.0 N in 19-mo-old control mice, 10.7 N in 19-mo-old LI-IGF-I−/− mice, 13.5 N in 6-mo-old control mice, and 11.5 N in 6-mo-old LI-IGF-I−/− mice.

**In vivo tibia loading.** The protocol for noninvasively loading the mouse tibia has been reported previously (1, 26, 37, 41). Briefly, while under inhalation anesthesia with Isoflurane (Forene; Abbot Scandinavia, Solna, Sweden), the right tibia of mice aged 6 (control, n = 11; LI-IGF-I−/−, n = 9) or 19 mo (control, n = 8; LI-IGF-I−/−, n = 7) was axially loaded on 3 alternate days/wk for 2 wk (days 1, 3, 5, 8, 10, and 12) for 40 cycles/day with a trapezoid waveform, with 10 s of rest between cycles. The loads were applied using a 3100 ElectroForce Test Instrument (Bose). The left tibia was not manipulated and was used as a nonloaded control to allow side-to-side comparisons for the effects of loading on bone modeling. The use of the contralateral limb as a control (1, 27) has been validated by comparing remodeling in the bones of limbs contralateral to those used in loading experiments with that in normal limbs of separate animals to which no loads had been applied (1, 27). All mice were allowed normal cage activity between loading sessions. The mice were euthanized after completing the 2 wk of loading (day 15), and their tibiae were dissected free of soft tissue, fixed for 48 h in Bürkhardt’s solution, and stored in 100% ethanol.

**High-resolution µCT.** Bone lengths were measured ex vivo with a slide caliper. Ex vivo measurements using high-resolution µCT analyses were performed using an 1172 µCT model (Bruker, Aartselaar, Belgium), as described previously (6, 18). The trabecular bone parameters were analyzed in the proximal metaphyseal region, whereas the cortical bone parameters were analyzed in the diaphyseal region of tibia (6, 18). For bone mineral density (BMD) analysis, the equipment was calibrated with ceramic standard samples.

**Three-point bending analyses.** The three-point bending test (span length 5.5 mm, loading speed 0.155 mm/s) at the midtibia was made using the Instron universal testing machine (Instron 3366; Instron, Canton, MA). Based on the recorded load deformation curves, the biomechanical parameters were acquired from raw files produced by Bluehill 2 software version 2.6 (Instron) with custom-made Excel macros.

**Statistical analyses.** All descriptive statistical results are presented as means (SE). Within-group differences were calculated using paired t-tests. Between-group differences were calculated using a two-way (age and genotype) analysis of variance (ANOVA). Linear regression analysis was used to calculate the relationship between peak dynamic load and strain at the gauge site. A two-tailed P < 0.05 was considered significant.

**RESULTS**

**Serum IGF-I, body weight, and length of tibia.** Liver-specific inactivation of the IGF-I gene was induced at 1 mo of age in female mice aged 6 mo at the loading experiments and at 12 mo of age in female mice aged 19 mo at the loading experiments. This resulted in reductions of serum IGF-I concentrations of 72% in 6-mo-old mice and 67% in 19-mo-old mice (Table 1). As could be expected, serum IGF-I was lower in the 19-mo-old control mice than in the 6-mo-old control mice.
Table 1. Reduced serum IGF-I but unchanged body weight and length of tibia in LI-IGF-I−/− mice

<table>
<thead>
<tr>
<th>Age, mo</th>
<th>Control</th>
<th>LI-IGF-I−/−</th>
<th>2-Way ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Serum IGF-I, ng/ml</td>
<td>274 (9)</td>
<td>77 (8)</td>
</tr>
<tr>
<td>19</td>
<td>216 (14)</td>
<td>80 (8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body weight, g</td>
<td>6</td>
<td>30.0 (2.0)</td>
<td>29.2 (1.3)</td>
</tr>
<tr>
<td>19</td>
<td>28.0 (1.7)</td>
<td>29.9 (2.1)</td>
<td>0.75</td>
</tr>
<tr>
<td>Length of tibia, mm</td>
<td>6</td>
<td>18.2 (0.1)</td>
<td>18.1 (0.1)</td>
</tr>
<tr>
<td>19</td>
<td>18.0 (0.1)</td>
<td>18.1 (0.1)</td>
<td>0.95</td>
</tr>
</tbody>
</table>

Values are given as means (SE). Liver-derived IGF-I was inactivated at 1 mo of age in 6-mo-old female mice (control, n = 11; LI-IGF-I−/−, n = 9) and at 12 mo of age in 19-mo-old female mice (control, n = 8; LI-IGF-I−/−, n = 7).

Table 2. Bone parameters in nonloaded (left) tibia as measured ex vivo using 3-point bending (mechanical strength) and high-resolution μCT (cortical and trabecular bone)

<table>
<thead>
<tr>
<th>Age, mo</th>
<th>Control</th>
<th>LI-IGF-I−/−</th>
<th>2-Way ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Maximal load, N</td>
<td>18.1 (0.6)</td>
<td>14.3 (0.5)</td>
</tr>
<tr>
<td>19</td>
<td>15.0 (0.7)</td>
<td>10.3 (0.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stiffness, N/mm</td>
<td>6</td>
<td>125.2 (6.6)</td>
<td>97.0 (9.6)</td>
</tr>
<tr>
<td>19</td>
<td>102.2 (5.9)</td>
<td>74.2 (9.1)</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>Area, mm²</td>
<td>6</td>
<td>0.63 (0.01)</td>
<td>0.57 (0.01)</td>
</tr>
<tr>
<td>19</td>
<td>0.53 (0.01)</td>
<td>0.49 (0.02)</td>
<td>0.001</td>
</tr>
<tr>
<td>vBMD, mg/cm³</td>
<td>6</td>
<td>1282 (6)</td>
<td>1264 (8)</td>
</tr>
<tr>
<td>19</td>
<td>1228 (9)</td>
<td>1188 (28)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Porosity, %</td>
<td>6</td>
<td>1.22 (0.07)</td>
<td>1.64 (0.15)</td>
</tr>
<tr>
<td>19</td>
<td>0.98 (0.05)</td>
<td>1.62 (0.39)</td>
<td>0.01</td>
</tr>
<tr>
<td>BV/TV, %</td>
<td>6</td>
<td>9.05 (0.34)</td>
<td>8.44 (0.83)</td>
</tr>
<tr>
<td>19</td>
<td>6.14 (0.41)</td>
<td>4.99 (0.46)</td>
<td>0.14</td>
</tr>
<tr>
<td>Trabecular thickness, μm</td>
<td>6</td>
<td>47 (1)</td>
<td>42 (2)</td>
</tr>
<tr>
<td>19</td>
<td>46 (2)</td>
<td>40 (1)</td>
<td>0.001</td>
</tr>
<tr>
<td>Trabecular number, 1/mm</td>
<td>6</td>
<td>1.91 (0.06)</td>
<td>2.02 (0.17)</td>
</tr>
<tr>
<td>19</td>
<td>1.33 (0.05)</td>
<td>1.24 (0.08)</td>
<td>0.93</td>
</tr>
<tr>
<td>Trabecular separation, mm</td>
<td>6</td>
<td>0.136 (0.000)</td>
<td>0.135 (0.001)</td>
</tr>
<tr>
<td>19</td>
<td>0.138 (0.000)</td>
<td>0.139 (0.000)</td>
<td>0.76</td>
</tr>
</tbody>
</table>

Values are given as means (SE). vBMD, volumetric bone mineral density; BV/TV, trabecular bone volume as a percentage of tissue volume; μCT, microcomputed tomography. Liver-derived IGF-I was inactivated at 1 mo of age in 6-mo-old female mice (control, n = 11; LI-IGF-I−/−, n = 9) and at 12 mo of age in 19-mo-old female mice (control, n = 8; LI-IGF-I−/−, n = 7).
2-way ANOVA analyses did not show any significant age ×
genotype interaction effects (Table 2), suggesting that the observed influences of genotype were similar in the two age
groups of mice.

Liver-derived IGF-I is dispensable for the osteogenic
response to loading. Representative high-resolution μCT images
from 6-mo-old mice are shown in Fig. 2. Mechanical loading
increased cortical bone area and BV/TV in the loaded right
control tibia compared with the nonloaded left control tibia
(Table 3), showing that the experimental procedures were
successful. The osteogenic response to loading on cortical bone
area, cortical bone mechanical strength, and BV/TV were not
affected by age (Table 3), suggesting an approximately similar
osteogenic response to mechanical loading in both age groups
of mice.

Importantly, LI-IGF-I−/− and control mice had a similar
bone anabolic response to mechanical loading in terms of
cortical bone area and BV/TV (Table 3). Furthermore, only the
LI-IGF-I−/− mice increased significantly in cortical bone
mechanical strength (maximal load at failure), as assessed using
three-point bending (Table 3). In line with these findings,
LI-IGF-I−/− mice had, compared with the control mice, a
significantly less marked increase in cortical porosity in re-
response to mechanical loading (Table 3). The two-way ANOVA
analyses did not show any significant age × genotype interac-
tion effects (Table 3), suggesting that the observed influences
of genotype were similar in the two age groups of mice.

DISCUSSION

Serum IGF-I concentration is decreased in patients with osteoporosis (42), and low levels of IGF-I in serum are asso-
ciated with increased fracture risk (3, 19). Although the under-
lying mechanisms are not fully clear, the phenotype of mice
with inactivation of liver-derived IGF-I is in accord with these
findings with cortical bone osteopenia and fragile bones (20,
24, 44). Recent studies show that conditional disruption of
locally produced IGF-I in osteoblasts (9) or osteocytes (12)
results in loss of the responsiveness to mechanical strain (9,
12). However, it is unknown whether circulating, liver-derived
IGF can affect the cells in bones that regulate the mechano-
tatic functions of bone. Here, we demonstrate that liver-derived
IGF-I is dispensable for the osteogenic response to mechanical
loading.

In most models of total or cell-specific knockout of IGF-I,
the role of IGF-I in adult life is difficult to evaluate due to the
possible effect of absence of IGF-I activity during pre- and
postnatal development (20). In the 6-mo-old and 19-mo-old
LI-IGF-I−/− mice of this study, the deficiency of endocrine
liver-derived IGF-I was induced at 1 and 12 mo of age,
respectively. Consequently, the mice developed normally but
then underwent a maintained selective inactivation of IGF-I in
hepatocytes, whereas IGF-I expression remained normal in the
peripheral tissues, as shown in several previous studies (7, 13,
23–25, 29–34, 36, 40).

One limitation of the present study is that dynamic cortical
histomorphometry was not performed. Furthermore, LI-IGF-I−/−
mice display compensatory increased GH levels (20, 23, 40).
Under nonloaded conditions, despite the compensatory increase
in GH secretion (20, 23, 40), the expression of IGF-I in bones is not
increased in the LI-IGF-I−/− mice compared with control mice
(20, 24). It is well known that IGF-I is upregulated in bone cells
in response to mechanical loading (8, 20), and it cannot be
excluded that this loading-induced upregulation of IGF-I in bones
could be enhanced in the LI-IGF-I−/− mice. It was not possible to
measure IGF-I locally in tibia in the present study, as the exper-
imental procedures included μCT and three-point bending. There-
fore, an additional study limitation is that we did not include
additional groups of LI-IGF-I−/− and control mice to study the
effect of mechanical loading on the local expression of IGF-I
in tibia. However, our aim was to investigate whether liver-
derived IGF-I has specific effects on the osteogenic response to
mechanical loading that is independent of the locally produced
IGF-I in bone cells.

Previous studies show that deficiency of liver-derived IGF-I
results in reduced cortical bone mass (20, 24, 44). We con-
ﬁrmed this cortical bone phenotype by comparing the non-
loaded tibia of LI-IGF-I−/− and control mice. Of special
interest are the 19-mo-old female mice with inactivation of
IGF-I in hepatocytes at 12 mo of age. This time span (12–19
mo of age) might resemble the age-related decline in serum
IGF-I observed in elderly humans more closely than early
inactivation of liver-derived IGF-I. In the present study, as also
seen in studies of 55-wk-old (24) and 2-yr-old mice (4),
cortical bone area decreased in the control mice as well as in
the LI-IGF-I−/− mice during aging. However, in the 6-mo-old

Fig. 2. LI-IGF-I−/− mice have tibia cross-sectional cortical bone area smaller
to control mice under nonloaded conditions but respond similarly to me-
chanical loading. Liver-derived IGF-I was inactivated at 1 mo of age in 6-mo-old
female mice (control, n = 11; LI-IGF-I−/−, n = 9) and at 12 mo of age in
19-mo-old female mice (control, n = 8; LI-IGF-I−/−, n = 7). Representative
high-resolution microcomputed tomography images from 6-mo-old mice are
shown. A: nonloaded control tibia. B: loaded control tibia. C: nonloaded
LI-IGF-I/−/− mice as well as the 19-mo-old LI-IGF-I/−/− mice, cortical area was lower than that in the age-matched control mice as assessed using μCT.

We observed markedly reduced cortical bone mechanical strength in the nonloaded LI-IGF-I/−/− tibia compared with the nonloaded control tibia independent of the age of the mice. Moreover, cortical vBMD was reduced and cortical porosity increased in both age groups of LI-IGF-I/−/− mice compared with the controls. Thus, our results suggest that the reduction of cortical mechanical strength was not due only to the reduced cortical bone area. Finally, the LI-IGF-I/−/− mice had slightly lower trabecular thickness compared with the control mice, which is in line with previous data in 2-yr-old mice deficient in liver-derived IGF-I (4).

The main objective of the present study was to investigate the importance of adult inactivation of liver-derived IGF-I in hepatocytes for the bone anabolic response to mechanical loading. We performed experiments in both young adult and old mice using an established experimental procedure that evaluates the loading-induced increases in bone parameters in the loaded right tibia compared with the corresponding values in the nonloaded left tibia. In both groups of control mice, cortical bone area and trabecular bone volume fraction (BV/TV) increased. This shows that the experimental procedures were successful that also the aged bone can adapt to mechanical strain, suggesting that physical exercise can produce loading-induced increases in bone mass in aged mice. Furthermore, the LI-IGF-I/−/− mice had responsiveness to loading similar to the controls in terms of cortical bone area and BV/TV independent of age. Importantly, this clearly shows that liver-derived circulating IGF-I is dispensable for both the cortical and trabecular bone anabolic response to mechanical loading in the presence of unchanged expression of locally produced IGF-I.

Table 4. The proposed role of liver-derived IGF-I and locally produced IGF-I (in osteoblasts and osteocytes) for bone characteristics

<table>
<thead>
<tr>
<th>Bone parameter</th>
<th>Deficiency of Liver-Derived IGF-I</th>
<th>Deficiency of Locally Produced IGF-I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone length</td>
<td>Unchanged</td>
<td>Reduced</td>
</tr>
<tr>
<td>Adult cortical bone mass</td>
<td>Reduced</td>
<td>Reduced</td>
</tr>
<tr>
<td>Bone anabolic response to mechanical loading</td>
<td>Unchanged</td>
<td>Reduced</td>
</tr>
</tbody>
</table>

Under normal (nonloaded) conditions, deficiency of liver-derived IGF-I and deficiency of locally produced IGF-I (in osteoblasts or osteocytes) (5, 22) result in reduced cortical bone mass. In contrast, only locally produced IGF-I is essential for the length of long bones (5, 22) as well as the bone anabolic response to mechanical loading (9, 12). Thus, liver-derived IGF-I cannot replace locally produced IGF-I in terms of the longitudinal growth of long bones or the osteogenic response to mechanical loading.
In response to mechanical loading, only the LI-IGF-I⁻/⁻ mice had an increase in maximal load at failure. Furthermore, the LI-IGF-I⁻/⁻ mice displayed a lower increase in cortical porosity and a more marked increase in trabecular thickness in response to mechanical loading. Although the effect on cortical bone mass is well defined in the present experimental setting, less is known of the effects on cortical porosity and mechanical strength. It has been demonstrated previously that mechanical loading increases cortical porosity (11). The recruitment of osteoblasts increases within a couple of days of mechanical loading (39), and a strong increase in bone formation is seen during the first weeks of loading (21). A new steady state, as indicated by a normalization of bone formation rate, is seen within 6 wk (21). Thus, the remodeling of bone is not completed after 2 wk of increased mechanical loading as in the present study, and therefore, it is not clear how the new steady-state conditions might be in the LI-IGF-I⁻/⁻ tibia or the control tibia. However, our results with increases in the amount of cortical as well as trabecular bone and increased mechanical strength in response to loading in the LI-IGF-I⁻/⁻ tibia clearly demonstrate that liver-derived, circulating IGF-I is dispensable for the bone anabolic response to mechanical loading.

In the presence of normal circulating IGF-I, previous studies demonstrated that disruption of locally produced IGF-I in osteoblasts or osteocytes results in reduced cortical bone mass (5, 22). Furthermore, in mice with global inactivation of IGF-I, the reduction of cortical bone mass is larger than that observed in mice with knockout of liver-derived or locally produced IGF-I (17). Therefore, both liver-derived IGF-I and locally produced IGF-I are needed to achieve a normal cortical bone mass, and they cannot replace each other. In contrast, liver-derived IGF-I is dispensable for the osteogenic response to mechanical loading, as shown in the present study, whereas locally produced IGF-I is required for a normal response to loading (9, 12). Based on these findings, we propose a model in which both liver-derived and locally produced IGF-I are essential for cortical bone mass at normal nonloaded conditions, whereas only locally produced IGF-I is needed for the bone anabolic response to mechanical loading (Table 4). However, double-knockout mice with deficiency of liver-derived IGF-I and total acid-labile subunit (ALS) (44), as well as triple-knockout mice lacking liver-derived IGF-I, total IGF-binding protein-3, and total ALS (45), have a much larger reduction (90–98%) of circulating IGF-I than LI-IGF-I⁻/⁻ mice. In contrast to the findings in the LI-IGF-I⁻/⁻ mice (20, 23), bone length is reduced in the double- or triple-knockout mice (44, 45). Based on a comparison between the essentially normal body length in mice with liver-specific IGF-I knockout (23, 43) and the reduced body length in the double- and triple-inactivated mice (44, 45), it has been postulated that a serum IGF-I threshold in the range of 10–25% of normal serum IGF-I exists, below which serum IGF-I levels associate with body growth (20). Therefore, whether a larger reduction of circulating IGF-I than that in the LI-IGF-I⁻/⁻ mice can also affect the bone anabolic response to mechanical loading needs to be determined in further studies.

Not only in old age but also in patients with osteoporosis as well as in patients with several other catabolic conditions, low serum IGF-I concentrations have been observed (3, 19, 20, 42). Although the importance of our findings for conditions in humans is not fully clear, our observation that IGF-I is dispensable for the bone anabolic response to mechanical loading could suggest that increased loading (i.e., physical exercise) can increase bone mass independent of the circulating level of IGF-I. Therefore, increased weight-bearing physical activity might, at least in part, counteract the consequences of low circulating IGF-I.

In conclusion, in 6-mo-old as well as in 19-mo-old mice, we confirm that liver-derived IGF-I is required for normal cortical bone mass. In addition, we show that deficiency of endocrine IGF-I results in increased cortical porosity. Furthermore, our results demonstrate that liver-derived IGF-I is dispensable for the bone anabolic response to mechanical loading in the presence of normal expression of locally produced IGF-I. Finally, our results suggest that mechanical loading (i.e., physical exercise) can also increase bone mass in old subjects with or without low circulating IGF-I.

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DISCLOSURES

There is nothing to disclose. None of the authors has a conflict of interest, financial or otherwise.

AUTHOR CONTRIBUTIONS


REFERENCES


AJP-Endocrinol Metab • doi:10.1152/ajpendo.00107.2016 • www.ajpendo.org
Liver-derived insulin-like growth factor I (IGF-I) is the principle source of IGF-I in blood but is not confined to the loaded bones.


