Relationships between bone mass and circulating leptin concentrations in Hutterites

Karen S. Wosje, a Teresa L. Binkley, a Heidi J. Kalkwarf, b and Bonny L. Specker a, *

a Ethel Austin Martin Program in Human Nutrition, South Dakota State University, Brookings, SD 57007, USA
b Cincinnati Children’s Hospital Medical Center, Division of General and Community Pediatrics, Cincinnati, OH 45229-3039, USA

Received 18 December 2003; revised 9 January 2004; accepted 14 January 2004

Abstract

A limited number of previous studies have shown inverse associations between bone mass or density and circulating leptin in humans. Relationships between bone mass and circulating leptin in Hutterites, who have elevated bone density, are unknown. Knowledge gained from studies in mice suggests that Hutterites exhibit traits consistent with a deficiency in circulating leptin or in leptin signaling. We examined relationships between whole body (WB) and regional (lumbar, total hip, femoral neck, trochanter) bone mineral content (BMC) by dual energy X-ray absorptiometry and circulating leptin in 249 Hutterites (137 female) ages 20–55 years and 72 similarly aged non-Hutterites (37 female). We tested the hypothesis that (1) Hutterites will have low circulating leptin concentrations for a given amount of body fat compared to non-Hutterites, and (2) controlling for body fat, there will be an inverse relationship between BMC and circulating leptin among Hutterites.

Hutterites had higher BMC than non-Hutterites at all skeletal sites after adjusting for site-specific bone area, age, and sex (P < 0.02). Hutterite females had higher leptin concentrations than non-Hutterite females [geometric mean and 95% confidence interval (CI): 18.38 (17.18, 19.67) vs. 14.30 (12.55, 16.28), P < 0.001] after adjusting for WB fat mass. Hutterite males also had higher leptin concentrations than non-Hutterite males [geometric mean and 95% CI: 6.53 (6.11, 6.98) vs. 5.62 (4.98, 6.35), P = 0.03] after adjusting for WB fat mass.

We used backward stepwise regression to determine significant (P < 0.10) covariates to include in models predicting WB and regional BMC among Hutterites (separately by sex). Subsequently, we entered leptin (log-transformed) to models to test for significance (P < 0.05). After adjusting for covariates, leptin concentration was not a significant predictor of BMC at any site, in either sex, among Hutterites. It is possible that genetic influences that interfere with hypothalamic leptin signaling, in a manner unrelated to adipocyte leptin production, contribute to elevated Hutterite bone density.

© 2004 Elsevier Inc. All rights reserved.

Keywords: Leptin; Bone mineral content; Bone mass; Bone density; Hutterite

Introduction

Hutterites form a religious group and believe in isolated communal living (i.e., in colonies) and self-sufficiency through technologically advanced and diverse agricultural practices. Children attend school at the colony through the eighth grade, then enter the physically demanding agricultural (e.g., livestock and grain production; males) or domestic (e.g., cleaning, house-painting, gardening; females) colony work rotation. The Hutterite population exhibits high prevalence of overweight [mean body mass index (BMI) of 27 kg/m² among adult females [1]] and normal reproductive function. We previously reported high bone density among female members of the Hutterite brethren [1]. We speculated that high levels of physical activity beginning in adolescence, adequate calcium nutrition over a lifetime, and genetic factors might enhance optimization of peak bone mass acquisition, resulting in above normal adult bone density among Hutterites.

The recent identification of leptin as a regulator of bone formation and of adiposity through appetite control suggests that genetically determined hormonal control might contribute to the high bone density in obese people. Leptin is the peptide hormone product encoded by the obese or leptin gene. Leptin primarily is produced by adipose tissue, and circulating leptin concentrations are
strongly correlated to indices of body fat in humans of different groups [2,3]. Leptin receptors are found in a variety of tissues but are highly concentrated in the hypothalamus, indicating that hormone action occurs primarily through neuroendocrine pathways [4]. Recently, several investigators have expanded research efforts focusing on the influence of leptin on body composition to include bone mineral in addition to fat mass [3,5,6]. Phenotypes for leptin-deficient (ob/ob) or leptin receptor-deficient (db/db) mice include obesity caused by disrupted appetite regulation and high bone mass despite hypogonadism [5]. The high bone mass phenotype was described as a dominant effect, because mice with only one allele of the leptin (ob/+ ) or leptin receptor gene (db/+ ) exhibited increased osteoblast function and high bone mass but were not obese or hypogonadic [5].

Higher body weight exerts beneficial effects on bone density and bone structural properties among human study populations [7–9]. In addition, mechanical bone strains can induce adaptations in bone size and geometry to increase bone strength [10]. Investigators often have assumed that this beneficial influence of higher body weight on bone properties primarily is attributable to bone adaptation to increased weight bearing (i.e., physical loading). Researchers are just beginning to characterize the extent to which leptin might exert influences on bone metabolism independent of its effects on obesity.

Blum et al. [11] recently reported that for a given percentage body fat, leptin was inversely associated with bone mineral density (BMD) among healthy premenopausal women. However, others have reported no association among premenopausal women [12,13] or inverse associations among both premenopausal women and males [13,14] between bone mass or density and circulating leptin when accounting for fat mass in the analyses. No previous studies on bone mass and circulating leptin have been conducted among adult human populations with high bone density. The Hutterite characteristics of high bone density, overweight, and normal reproductive function are consistent with a condition in which leptin concentrations or leptin signaling are deficient but not absent. The purpose of the current study was to investigate the relationships between both whole body (WB) and regional bone mineral content (BMC, bone mass, g/cm²) and circulating leptin concentration in an eastern South Dakota population of Hutterites. We hypothesized that:

**Hypothesis 1**: Hutterites will have low circulating leptin concentrations for a given amount of fat mass compared to non-Hutterites.

**Hypothesis 2**: Controlling for body fat and other covariates, the relationship between BMC and circulating leptin will be inverse among Hutterites.

**Materials and methods**

**Participants**

Participants included Hutterites ages 20–55 years that were enrolled before July 2002 in a longitudinal study designed to determine effects of a rural lifestyle on bone health [South Dakota Rural Bone Health Study (SDRBHS)]. Participants provided fasted blood samples and diet and activity information, received baseline whole body and regional DXA scans, and did not meet exclusion criteria. The protocol was approved by the South Dakota State University Human Subjects Review Board. Each participant provided written informed consent. Because only baseline data were used, the present study was cross-sectional. Reasons for exclusion from the present study were as follows: currently pregnant, pregnant within the last 6 months, currently lactating, weaning (defined as having lactated within the previous 12 months), history of hyper- or hypoparathyroidism, organ transplant, diabetes type I or II, thyroid disease, cystic fibrosis, cancer, kidney disease, or liver disease. Among 361 Hutterites ages 20–55 from the SDRBHS, 36 were lactating, weaning, or pregnant, 5 did not provide diet and activity information, 22 were excluded for medical reasons, and 34 did not have fasted plasma samples. Because only 15 of 152 females were estrogen-deplete (i.e., postmenopause and not receiving hormone replacement therapy), it was not possible to adequately examine estrogen effects. Therefore, only estrogen-replete females were included. Estrogen-replete females were identified as those who were either premenopausal (n = 118) or postmenopausal and currently receiving hormone replacement therapy (n = 17). Two females without an intact uterus who reported having at least one ovary and did not report having reached menopause were classified as estrogen-replete. The final number of individuals included in the present analyses is therefore 249 (137 females). One male did not have a whole body DXA scan due to his high body weight. In addition, two females did not have DXA hip scans.

For testing Hypothesis 1, we identified 37 estrogen-replete, non-Hutterite females and 35 non-Hutterite males who were of similar age, had fasted plasma leptin measurements, and were enrolled in the SDRBHS before July 2002. Forty-three percent (16/37) of the non-Hutterite females and 63% (22/35) of the non-Hutterite males had spent at least 75% of their lives involved in farming or ranching (i.e., rural lifestyle).

**Bone and body composition measurements**

Dual energy X-ray absorptiometry (QDR4500A, Hologic Inc., Waltham, MA) was used to assess whole body, lumbar, and hip (total hip, femoral neck, and trochanter) BMC. The coefficients of variation (CV) for whole body,
lumbar, and total hip BMC by DXA are <1%. All DXA scans were conducted and analyzed by a trained, certified technician.

Blood collection and plasma leptin assay

Fasted blood samples were drawn, centrifuged, and processed following standard operating procedures. Plasma samples of 1 ml were stored at −70°C. Human leptin assays were performed by Linco Inc. (St. Charles, MO) using a radioimmunoassay (RIA) kit. Samples were sent in two separate batches via overnight delivery on dry ice, and the same RIA method was used to analyze both batches. Linco Inc. reports intra- and interassay CVs of <5%. Sensitivity of the Linco Inc. human leptin RIA is 0.5 ng/ml when using a 1-ml sample size.

Potential covariates

Dietary intake

Study personnel conducted individual interviews to obtain dietary intake, including nutritional supplements, for the previous 24 h. Food models depicting portion sizes were used to facilitate portion estimation. Intakes of calcium and vitamin D were calculated using Nutritionist V software (First Data Bank, San Bruno, CA).

Physical activity

A modified Seven-Day Physical Activity Recall (SDPAR) [15] was obtained via individual interview by study personnel. The SDPAR was modified to include examples of physical activities common to Hutterites (e.g., digging in the garden, house painting). The SDPAR data were used to calculate percentage of time spent in vigorous plus moderate activity. Quartiles for percentage of time spent in vigorous plus moderate activity per day (“physical activity quartiles”) were as follows: 0 to <12.2% for Quartile 1, 12.2 to <20.8% for Quartile 2, 20.8 to <30.9% for Quartile 3, and >30.9% for Quartile 4. There were three activity records omitted, because the SDPAR form was not completed properly.

Anthropometric and strength measurements

Height without shoes was measured to the nearest 0.5 cm using a standard stadiometer. Weight with light clothing was measured to the nearest 0.1 kg using a digital Seca scale (Model 770). Body mass index was calculated as kg/m². Grip strength was measured using a dynamometer (GRIP-D) instrument. The highest recorded grip strength from three trials was used. There were three females who refused weight measurement and four females who refused grip strength measurement.

Statistical analyses

Statistical analyses were carried out using JMP software Version 4 (SAS Institute, Cary, NC). Outcome variables (whole body, lumbar, total hip, femoral neck, and trochanter BMC) were checked for normality before analyses, and no data transformations were required. Plasma leptin data were highly positively skewed; therefore, log-transformed leptin values were used in all analyses.

Student t-test was used to examine differences between Hutterites and non-Hutterites for independent variables. For testing Hypothesis 1, we used ANOVA to determine whether Hutterites had normal, reduced, or elevated circulating leptin concentrations compared to non-Hutterites; ANCOVA was used to control for whole body fat mass. To determine whether Hutterites had greater BMC for a given bone size and age, we used ANCOVA to control for site-specific bone area, age, and sex.

Table 1

<table>
<thead>
<tr>
<th></th>
<th>Females</th>
<th></th>
<th>Males</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hutterite</td>
<td>Non-Hutterite</td>
<td>Hutterite</td>
<td>Non-Hutterite</td>
</tr>
<tr>
<td>Number</td>
<td>137</td>
<td>37</td>
<td>112</td>
<td>35</td>
</tr>
<tr>
<td>Age (year)</td>
<td>36 ± 11</td>
<td>42 ± 10*</td>
<td>36 ± 9</td>
<td>44 ± 10**</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>72 ± 14</td>
<td>76 ± 20</td>
<td>92 ± 15</td>
<td>94 ± 18</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>162 ± 5</td>
<td>165 ± 6*</td>
<td>177 ± 5</td>
<td>179 ± 8</td>
</tr>
<tr>
<td>WB percentage fat</td>
<td>34.3 ± 6.8</td>
<td>35.4 ± 5.9</td>
<td>22.9 ± 5.7</td>
<td>24.6 ± 6.2</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27 ± 6</td>
<td>28 ± 6</td>
<td>30 ± 5</td>
<td>29 ± 5</td>
</tr>
<tr>
<td>Grip strength (kg)</td>
<td>33 ± 6</td>
<td>29 ± 7*</td>
<td>57 ± 9</td>
<td>51 ± 9**</td>
</tr>
<tr>
<td>Leptin (ng/ml)a</td>
<td>17.9 (15.9, 20.1)</td>
<td>15.7 (12.7, 19.4)</td>
<td>6.3 (5.5, 7.3)</td>
<td>6.4 (4.9, 8.4)</td>
</tr>
<tr>
<td>Leptin (ng/ml)b</td>
<td>18.4 (17.2, 19.7)</td>
<td>14.3 (12.6, 16.3)**</td>
<td>6.5 (6.1, 7.0)</td>
<td>5.6 (5.0, 6.3)***</td>
</tr>
<tr>
<td>Calcium intake (mg/day)</td>
<td>1007 ± 608</td>
<td>1014 ± 878</td>
<td>929 ± 583</td>
<td>1139 ± 778</td>
</tr>
<tr>
<td>Vitamin D intake (IU/day)</td>
<td>257 ± 359</td>
<td>290 ± 311</td>
<td>175 ± 206</td>
<td>231 ± 212</td>
</tr>
</tbody>
</table>

Data are mean ± SD.

Student t-test was used to compare Hutterites and non-Hutterites (within sex) for all variables.
a Geometric mean and 95% CI of the mean, unadjusted for fat mass.
b Geometric mean and 95% CI of the mean, adjusted for fat mass.
* P ≤ 0.01 compared to Hutterites (within sex).
** P ≤ 0.001 compared to Hutterites (within sex).
*** P = 0.03 compared to Hutterites (within sex).
Fig. 1. Circulating leptin concentrations in Hutterites and non-Hutterites. Leptin values are geometric means and 95% CIs of the mean, determined after adjusting for whole body fat mass; ***P < 0.001 (females) and *P = 0.03 (males) for difference between Hutterites and non-Hutterites.

Because of the known sexual dimorphism in circulating leptin concentrations, statistical analyses for testing Hypothesis 2 were performed separately by sex. Whole body fat mass and site-specific bone area to partially account for the effect of bone size were forced into all models predicting BMC. Other potential covariates were selected for each BMC outcome variable with a backward stepwise regression procedure using significance level \( P \leq 0.10 \); potential covariates were age, height, whole body lean mass, physical activity quartile, grip strength, calcium intake, and vitamin D intake. Subsequently, leptin was added to each model to determine statistical significance (\( P \leq 0.05 \)).

Data are presented as least-squares mean ± SEM or geometric mean and 95% confidence interval (CI) of the mean, as indicated.

Results

Anthropometrics, strength measurements, and nutrient intakes among Hutterite and non-Hutterite females and males are presented in Table 1. Thirty-six percent (\( n = 49 \)) of Hutterite females and 53% (\( n = 19 \)) of non-Hutterite females reported spending at least 5 h/day engaged in vigorous and moderate activity (\( P = 0.03 \)). Seventy-one percent (\( n = 80 \)) of Hutterite males and 62% (\( n = 21 \)) of non-Hutterite males reported spending at least 5 h/day engaged in vigorous and moderate activity (\( P = 0.07 \)).

One-way ANOVA revealed no significant difference between Hutterite and non-Hutterite females in mean leptin values, unadjusted for fat mass [geometric means and 95% CI: 17.9 (15.9, 20.1) vs. 15.7 (12.7, 19.4)]. Hutterite and non-Hutterite females had similar mean BMI, whole body fat mass, and whole body percentage fat. Despite the lack of difference between Hutterite and non-Hutterite females in body fat, circulating leptin concentrations were elevated in Hutterite compared to non-Hutterite females after adjusting for whole body fat mass [Fig. 1; geometric means and 95% CI: 18.4 (17.2, 19.7) vs. 14.3 (12.6, 16.3); \( P \leq 0.001 \)]. Similar findings were apparent when adjusting for whole body percentage fat.

In males, one-way ANOVA revealed no significant difference between Hutterite and non-Hutterite females in mean leptin values, unadjusted for fat mass [geometric means and 95% CI: 6.3 (5.5, 7.3) vs. 6.4 (4.9, 8.4)]. Hutterite and non-Hutterite males had similar mean BMI, whole body fat mass, and whole body percentage fat. As with females, leptin values were elevated in Hutterite compared to non-Hutterite males after adjusting for whole body fat mass [Fig. 1; geometric means and 95% CI: 6.5 (6.1, 7.3) vs. 5.6 (5.0, 6.3); \( P = 0.03 \)]. Similar findings were apparent when adjusting for whole body percentage fat.

Table 2 shows least-squares means for whole body, lumbar, total hip, femoral neck, and trochanter BMC for Hutterites and non-Hutterites by sex. Hutterites had higher BMC at all sites (\( P \leq 0.02 \)), and the percentage differences between Hutterites and non-Hutterites ranged from 1.4% (whole body; females) to 12.1% (trochanter; males).

Table 3 summarizes statistical models predicting whole body, lumbar, total hip, femoral neck, and trochanter BMC. After accounting for whole body fat mass, site-specific bone area, and significant covariates selected by the backward stepwise regression procedure, leptin did not contribute significantly to explaining variation in BMC in either sex at any skeletal site. Similar findings were apparent when whole body percentage fat was substituted for whole body fat mass and site-specific bone area, age, and Hutterite×Sex (interaction not significant; \( P > 0.07 \) for all sites).

### Table 3: DXA bone mineral content for Hutterites and non-Hutterites

<table>
<thead>
<tr>
<th>Number</th>
<th>Females</th>
<th>Males</th>
<th>( P ) value*</th>
<th>( P ) value for*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole body BMC (g)</td>
<td>2675 ± 17</td>
<td>2637 ± 29</td>
<td>1.4</td>
<td>2630 ± 20</td>
</tr>
<tr>
<td>Lumbar BMC (g)</td>
<td>73.54 ± 0.75</td>
<td>70.77 ± 1.32</td>
<td>3.9</td>
<td>69.62 ± 0.82</td>
</tr>
<tr>
<td>Total hip BMC (g)</td>
<td>39.86 ± 0.57</td>
<td>38.54 ± 0.85</td>
<td>3.4</td>
<td>41.70 ± 0.62</td>
</tr>
<tr>
<td>Femoral neck BMC (g)</td>
<td>4.66 ± 0.06</td>
<td>4.54 ± 0.11</td>
<td>2.6</td>
<td>5.17 ± 0.07</td>
</tr>
<tr>
<td>Trochanter BMC (g)</td>
<td>9.88 ± 0.13</td>
<td>9.37 ± 0.23</td>
<td>5.4</td>
<td>10.37 ± 0.15</td>
</tr>
</tbody>
</table>

Values are least-squares means from model containing site-specific bone area, age, and Hutterite×Sex (interaction not significant; \( P > 0.07 \) for all sites).

* \( P \) values are from main effects model containing site-specific bone area, age, sex, and Hutterite.
Table 3
Summary of multiple regression models for predicting BMC among Hutterite females and males

<table>
<thead>
<tr>
<th></th>
<th>Females</th>
<th>Males</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$R^2$</td>
<td>$P$ value for</td>
</tr>
<tr>
<td></td>
<td>fat mass</td>
<td>for leptin</td>
</tr>
<tr>
<td>Whole body BMC (g)</td>
<td>0.78</td>
<td>0.03&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>+ leptin</td>
<td>0.78</td>
</tr>
<tr>
<td>Lumbar BMC (g)</td>
<td>0.68</td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td>+ leptin</td>
<td>0.68</td>
</tr>
<tr>
<td>Lumbar BMC (g)</td>
<td>0.68</td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td>+ leptin</td>
<td>0.68</td>
</tr>
<tr>
<td>Total hip BMC (g)</td>
<td>0.62</td>
<td>0.05&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>+ leptin</td>
<td>0.62</td>
</tr>
<tr>
<td>Femoral neck BMC (g)</td>
<td>0.71</td>
<td>&lt;0.001&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>+ leptin</td>
<td>0.71</td>
</tr>
</tbody>
</table>

<sup>a</sup> Whole body fat mass, site-specific bone area, and variables from the following list, which were significant at $P < 0.10$ before entering leptin, were retained as covariates: age, height, physical activity quartile, grip strength, whole body lean mass, calcium intake, and vitamin D intake.

<sup>b</sup> Regression coefficient was positive.

<sup>c</sup> Regression coefficient was negative.

Discussion

We proposed that the traits of high bone density, overweight, and normal reproductive function were indicative of a high prevalence among Hutterites of a condition in which leptin signaling is deficient but not absent. Thus, in Hypothesis 1, we presumed that low circulating leptin concentrations were consistent with or resulted in diminished hypothalamic leptin signaling. However, we observed elevated leptin concentrations in Hutterites compared with non-Hutterites in both sexes when adjusting for fat mass. Banks and Farrell [16] reported that transport of leptin across the blood–brain barrier is impaired in normal obese mice (i.e., mice with elevated circulating leptin concentrations) compared to nonobese controls, suggesting that obesity induces hypothalamic leptin resistance. Since we found no relationships between BMC and circulating leptin concentrations (see next paragraph), it is unlikely that hypothalamic leptin resistance, induced by adipocyte leptin overproduction, exists among Hutterites and contributes to their high bone mass. However, it remains possible that genetic influences to impair hypothalamic leptin signaling, in a manner unrelated to adipocyte leptin overproduction, exist among Hutterites.

Our Hypothesis 2 that, for a given fat mass, BMC and leptin would be inversely related among Hutterites was not confirmed. We developed our hypothesis based on previous reports of negative associations between BMD and leptin among estrogen-replete females [11,14] and males [13,14]. Our results are not in conflict with all previous reports in the literature, because some investigators also have shown no relationship between whole body [12,17,18], lumbar [12,13], hip [12–14], or radius [13] bone mass or density and circulating leptin when fat mass was taken into account. Because our findings indicate that circulating leptin concentrations do not significantly contribute to explaining variation in whole body or regional BMC in a population that exhibits high average areal bone density at several skeletal sites and because previous reports on relationships between bone and leptin are inconsistent, we conclude that there remains little convincing evidence that BMC and circulating leptin are related, independent of body fat, in humans.

The influence of circulating leptin on BMC is difficult to ascertain for several reasons. In the present study, we determined that Hutterites had elevated circulating leptin concentrations relative to fat mass, and therefore both leptin and fat mass were included in statistical models predicting BMC. Since fat cells are the primary producers of leptin, any relatively small but perhaps statistically and clinically significant, independent effect of leptin on BMC might be undetectable in models that include both fat mass and leptin.

Based on accumulated evidence, Reseland and Gorde-ladze [19] suggested that leptin controls bone by (1) central suppressive mechanisms and (2) direct stimulatory actions. Work by Ducy et al. [5], in which the response of ob/ob mice to intracerebroventricular leptin injection was decreased bone formation and bone loss, clearly indicates that leptin is involved in hypothalamic control of bone formation. Other studies in ob/ob mice suggest that leptin injected intraperitoneally or subcutaneously acts directly on osteoblasts in bone tissue to increase femur length and bone mass [20] and to stimulate cortical bone formation [21]. The relevance of circulating leptin concentrations to the function of these two mechanisms is unclear.

Ducy et al. [5] demonstrated using histomorphometry that leptin-deficient (ob/ob) and leptin receptor-deficient (db/db) mice have a high bone mass phenotype; however, there are contrary reports indicating that ob/ob mice have short stature [20], that db/db mice are osteopenic [22], and that fa/fa rats (which lack functioning leptin receptors) have decreased trabecular number compared with lean controls [23]. Reasons for these differences in the descriptions of phenotypes for genetically obese mice are unclear; nevertheless, evidence indicates that leptin might act centrally to suppress and locally to stimulate bone formation [19]. Among Hutterites, elevated circulating leptin and a genetic hypothalamic leptin resistance might combine to promote high bone density.

We recognize that conclusions drawn from this study among Hutterites are not likely to be relevant to genetically heterogeneous populations. However, we speculate that continued elucidation of factors influencing bone, in a population with demonstrated bone density advantages, will
provide valuable insight into potential intervention or therapeutic strategies.

There are caveats associated with using DXA to assess bone health status, because the measurement obtained is not a volumetric bone density. By controlling for bone area in all statistical models predicting BMC, we eliminated some of the difficulty of interpreting DXA, BMC, or BMD results that occur when larger bones are compared to smaller bones. Because such caveats exist, further examination of circulating leptin on volumetric cortical and trabecular bone density, cortical thickness, endosteal and periosteal circumferences of long bone shafts, and quantifiable bone strength indices would be beneficial. Studies on relationships between peripheral quantitative computed tomography (pQCT)-derived bone size, volumetric density, and geometric attributes are feasible and necessary to complement DXA-derived findings.

In conclusion, we have confirmed that a sexual dimorphism in circulating leptin exists among a population of Hutterites with high bone density. Circulating leptin concentrations do not contribute significantly to explaining variation in whole body, lumbar, and hip BMC among Hutterites. Hutterites have elevated circulating leptin concentrations for a given amount of fat mass, which might increase their susceptibility to developing hypothalamic leptin resistance. However, our results do not allow us to conclude that hypothalamic leptin resistance, induced by high circulating leptin concentrations, exists and contributes to high bone mass among Hutterites. It would be necessary—but not feasible—to directly measure leptin transport across the blood–brain barrier to determine if leptin resistance is influencing bone among Hutterites. The genetic homogeneity of the Hutterite population suggests that their apparently elevated bone density primarily is due to inherited factors or gene–environment interactions. We cannot rule out that there are genetic influences that interfere with the hypothalamic leptin signaling pathways in a manner that is unrelated to adipocyte leptin overproduction among Hutterites.

Acknowledgments

Foremost, we gratefully acknowledge the willingness and cooperation of study participants. We also would like to acknowledge all Ethel Austin Martin Program staff and graduate students, without whom this study could not have been conducted. This study was funded in part by the National Institutes of Health under R01-AR47852.

References