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Low Bone Mineral Density is a Common Finding in Patients with Homocystinuria

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Abstract

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Homocystinuria (HCU) due to deficiency of cystathionine beta-synthetase is associated with increased plasma levels of homocysteine and methionine and is characterized by developmental delay, intellectual impairment, ocular defects, thromboembolism and skeletal abnormalities. HCU has been associated with increased risk for osteoporosis in some studies, but the natural history of HCU-related bone disease is poorly understood. The objective of this study was to characterize bone mineral density (BMD) measured by dual energy X-ray absorptiometry (DXA) in a multi-center, retrospective cohort of children and adults with HCU. We identified 19 subjects (9 males) aged 3.5 to 49.2 years who had DXA scans performed as a part of routine clinical care from 2002–2010. The mean lumbar spine (LS) BMD Z-score at the time of first DXA scan in this cohort was -1.2 ($\pm$ SD of 1.3); 38% of participants had low BMD for age (as defined by a Z-score < -2). Homocysteine and methionine were positively associated with LS BMD Z-score in multiple linear regression models. Our findings suggest that low BMD is common in both children and adults with HCU and that routine assessment of bone health in this patient population is warranted. Future studies are needed to clarify the relationship between HCU and BMD.

Keywords

Homocystinuria; Osteoporosis; Dual Energy X-ray Absorptiometry; Bone Mineral Density

Introduction

Homocystinuria (HCU) (OMIM 236200) is an autosomal recessive disorder in the metabolism of sulfur containing amino acids that is caused by mutations in *CBS*, which encodes the pyridoxine (vitamin B6)-dependent enzyme cystathionine beta-synthase (CBS). [1] Deficient cystathionine beta-synthase activity disrupts methionine metabolism and results in accumulation of homocysteine and methionine in the blood and urine. Clinical manifestations are variable and can include developmental delay and intellectual disability, ectopia lentis, myopia, thromboembolism, and skeletal anomalies such as tall stature and long limbs. Therapeutic reduction of homocysteine levels via methionine or protein restricted diet, betaine administration, or pyridoxine administration can improve clinical outcomes. [2, 3]

The skeletal features of HCU include scoliosis, vertebral changes, genu valgum, metaphyseal widening, sternal deformities, arachnodactyly [4] and reduced bone density.[4–10] Two previous studies that used dual energy X-ray absorptiometry (DXA), the current standard for bone densitometry in the clinical setting, to assess bone mineral density (BMD) in patients with HCU produced conflicting results. A study in adults found low BMD[11] while a second small study in Korean children reported normal BMD.[12] The objective of this study was to assess BMD and markers of HCU control in a cohort of pediatric and adult HCU patients through analysis of existing DXA scans and biochemical results obtained during routine clinical care.

Methods

Participants

A retrospective chart review identified 19 subjects with HCU due to CBS deficiency who had undergone clinical DXA bone densitometry at The Children's Hospital of Philadelphia, Children's Hospital of Colorado, or The Hospital of The University of Pennsylvania between July 2002 and January 2010. DXA scans were excluded from analysis if subjects had received glucocorticoid treatment in the previous 6 months or had ever previously received specific therapy (e.g. bisphosphonates) that might alter BMD. This study was approved by the Institutional Review Boards at The Children's Hospital of Philadelphia, The Children's Hospitalin Aurora, Colorado, and the University of Pennsylvania.

Bone Densitometry

Whole body, lumbar spine (LS), and hip DXA bone mineral content (BMC) and BMD were measured using Hologic (Hologic, Inc., Bedford MA) or General Electric/Lunar (GE; General Electric, Fairfield CT) densitometers. Z-scores were extracted from the clinical reports that had been generated using manufacturer's reference data. We analyzed Z-scores rather than T-scores because our primary objective was to evaluate BMD relative to an age-matched reference population. The results of BMD and BMC analyses for pediatric participants aged 5–20 years who were studied with Hologic densitometers s (software version 12.1 or higher) were converted into age-, sex-, and race-specific Z-scores and adjusted for height Z-score using reference data from the Bone Mineral Density in Childhood Study (BMDCS).[13] There is no similar validated method for height adjustment of BMC and BMD using older Hologic or GE/Lunar data. Low BMD was defined as a BMD Z-score of -2 . [14]

Biochemical parameters

We analyzed biochemical markers of HCU control (total homocysteine and methionine) and biomarkers related to mineral metabolism [25-hydroxy vitamin D (25OH-D), calcium] that had been obtained at the time of the DXA scan as recorded in patient clinical medical records. Total homocysteine quantification was determined in plasma or serum by a variety of methods dependent upon the assaying laboratory. Methods include liquid chromatography-tandem mass spectrometry (LC-MS/MS) stable isotope analysis, gas chromatograph-mass spectrometry (GCMS) stable isotope analysis, chemiluminescence immuno metric assay, and VITROS Chemistry Products HCY2 reagent spectrophotometric assay (Ortho Clinical Diagnostics, Raritan, NJ, USA). Amino acids quantification was determined in either plasma or serum by a variety of methods dependent upon the assaying laboratory. Amino acids present in plasma or serum is separated by LC-MS/MS or ion-exchange chromatography and the concentration of amino acids was established by comparison to that of respective internal standards determined previously from calibration standards. Sensitivity analyses were performed using homocysteine and methionine values that represented the average plasma levels for these markers over the entire study period.

Statistical Methods

Parametric data are reported as mean ($\pm$ standard deviation) and compared using t-tests; non-parametric data are reported as median (interquartile range) and compared using Wilcoxon rank-sum test. Proportions were compared using chi-square test. Correlations were assessed by Spearman's rho. Multivariable linear regression was used to examine raw and adjusted associations between BMD outcomes and biochemical markers of HCU metabolic control. Non-parametric variables were log transformed prior to regression analysis. All statistical analyses were performed with Stata 12 software (StataCorp, L.P., College Station, TX). Statistical significance was defined using a 2-sided p value <0.05 for all analyses.

Results

The clinical characteristics of the 19 study subjects are presented in Table 1 and Supplemental Table 1. The sample consisted of subjects aged 3.5 to 49.2 years at first DXA scan and included 13 children (68%) who were less than 21 years of age. An initial diagnosis of HCU was ascertained by newborn screen (28%), family history (28%), or clinical presentation with features such as ectopia lentis, thromboembolic event, or typical body habitus (44%). Median time from diagnosis to first DXA scan was 4.1 years (IQR: 2 to 14.1). Median height Z-score at time of DXA was 0.9 (range -2.6 to 2.8). Three subjects had a history of 5 fractures; 1 fracture was an atraumatic vertebral compression fracture while the other fractures had occurred in the setting of trauma. Three subjects (16%) had documented vitamin D insufficiency [25-hydroxy vitamin D <30 ng/mL (75 nmol/L)] and none had vitamin D deficiency [25-hydroxy vitamin D <20 ng/mL (50 nmol/L)] at time of DXA. At time of the first DXA scan, the median levels of plasma homocysteine was 59.2 μ mol/L (IQR: 38.5 to 152.1), and plasma methionine was 477.6 nmol/mL (IQR: 63.8 to 684.4). 15 subjects were following a protein-restricted diet and 16 participants were prescribed betaine supplementation. Only 1 participant was pyridoxine-responsive.

A total of 39 DXA scans in 19 subjects were reviewed. DXA scans were performed most commonly at the lumbar spine (LS) (32 scans), followed by hip (19 scans), and total body less head (4 scans). The majority of scans (27/39, 69%) were performed in subjects under 21 years of age. At the time of first DXA scan, the LS BMD Z-score was -1.2 ± 1.3 (mean $\pm$ SD) and total hip BMD Z-score was -0.89 ± 0.4 ; both were significantly lower than 0 (the expected mean Z-score in the population) with $p=0.002$ and 0.02 , respectively (Table 2). The LS BMD Z-score at diagnosis was -1.26 ± 1.4 in pediatric patients aged less than 21 years and -1.06 ± 1.1 in adults. In total, 38.5% of pediatric subjects (5/13) and 31.6% (6/19) of the entire cohort met the criteria for low BMD for age (BMD Z-score ≤ -2) on at least one DXA scan. By contrast, approximately 2.5% of individuals in a normal population would be expected to fall 2 standard deviations (i.e. Z-score < -2) below the mean.

Correlations between LS BMD Z-scores and biochemical markers of HCU are shown in Table 3. There was a weak positive correlation between average LS BMD Z-score and average homocysteine (Spearman's rho 0.499, $p=0.05$) and average methionine (Spearman's rho 0.489, $p=0.05$) levels over the entire study period. Positive correlations were also present between LS BMD Z-score and both homocysteine and methionine level at time of first DXA, but these associations failed to reach significance. Similar associations were observed

when linear regression was used to examine relationships between LS BMD Z-score and markers of HCU (Table 4). Homocysteine and methionine levels were positively associated with LS BMD Z-score at time of first DXA scan, after adjustment for sex, age, and height.

Longitudinal BMD data were available at the LS for 9 subjects. The mean change in LS BMD Z-score was 0.16 ± 0.81 (range: -1.3 to 1.5) over a period of 2.5 ± 1.4 years (range: 1 to 4.1 years). This included 5 subjects who had increases in BMD Z-score and 4 subjects who had decreases in BMD Z-score over the study period. There was no difference in age, sex, or markers of HCU control (baseline, average, or change) among subjects who had decreases in LS BMD Z-scores compared to those who had increases. Additionally, there were DXA scans in 6 pediatric participants that could be adjusted for height Z-scores [median height Z-score of 0.86 (IQR: -0.66 to 1.3): median LS BMD Z-score at time of first DXA scan in these participants prior to adjustment for height Z-score was -0.71 (IQR: -2.3 to -0.28), which was reduced after adjustment for elevated height Z-score to -1.03 (IQR: -2.16 to 0.52).

Discussion

Our multi-center clinical study in a mixed population of pediatric and adult patients found that low BMD was common in subjects with HCU. Although our data are consistent with previous studies in adults, to our knowledge this is the first report of low BMD in the pediatric HCU population. Our results are in contrast to a previous retrospective study of 5 Korean children that identified a mean LS BMD Z-score of -0.6 and no instances of individuals with Z-scores ≤ -2 . [12] Our study suggests that accrual of bone mass during childhood and adolescence, a critical period for skeletal growth, is deficient in HCU, and may negatively impact attainment of peak bone mass.

The potential mechanisms leading to low BMD and skeletal fragility in HCU are unclear. Homocysteine may impair bone strength directly, as evidenced by findings that greater homocysteine levels have been associated with greater fracture risk even in patients who do not have HCU. [15, 16] There is *in vivo* and *in vitro* evidence that homocysteine may weaken bone through a reduction in collagen cross-link formation. [17] Other proposed mechanisms include impaired formation of bone matrix as a result of homocysteinylolation of fibronectin [18] and homocysteine-mediated increases in osteoclastic bone resorption. [19] Regrettably, due to the retrospective nature of our study we lack bone turnover markers or bone histomorphometry that could address these hypotheses.

Our finding of a positive association between DXA BMD Z-scores and homocysteine and methionine was unexpected. One possibility is that individuals with lower levels of homocysteine, and methionine were more adherent to a protein restricted diet and therefore consumed less calcium-containing dairy products. Methionine was shown to have anti-osteoclastogenic properties in an animal model, [20] which could increase BMD as a result of lower bone resorption. Additionally, methionine levels increase in response to betaine therapy, [21] therefore the positive relationship between BMD Z-scores and methionine could be representative of medication adherence and HCU control. Our sample size was too small to fully explore the impact of betaine or other aspects of treatment on the relationships

between homocysteine, methionine, and BMD. Participants in our study had normal serum calcium levels, but the biochemical markers needed to more fully assess whole body calcium status as well as bone turnover and growth are not routinely checked in clinical practice and were unavailable for analysis here.

Our study has several limitations. First, this was a retrospective study in a clinically heterogeneous population and limited to clinically available data. Potentially interesting characteristics including participant IQ, molecular genotype, and detailed dietary records were not routinely obtained and/or documented and will need to be investigated in future prospective studies. Of particular interest would be an analysis of genotype/phenotype correlations between CBS mutation and BMD; which if present could explain the discordant findings of our study compared to the previous report published by Lim, et al. [12]. Second, BMC and BMD were acquired with two different DXA platforms over a 9 year period. Because of known differences between DXA platforms and the reference populations used by the two manufacturers to calculate Z- and T-Scores, direct comparisons within our cohort may be limited.[22] Nevertheless, DXA is currently the most widely used method of assessing BMD and fracture risk in the clinical setting and our results confirm that low BMD is a common finding on clinical DXA reports in patients with HCU. Additionally, DXA cannot differentiate between trabecular and cortical bone compartments, nor assess bone material quality, which may be important considerations for future studies aimed at elucidating the mechanisms of skeletal disease in HCU. Finally, blood samples for metabolic tests were obtained at different times of day and therefore may be affected by diurnal variation and fasting state.[23, 24]

On the other hand, our study has important strengths. We found significant inconsistencies in the clinical monitoring of bone health in patients with HCU, both within and across institutions. Notably, there was considerable variability in the skeletal sites assessed by DXA. And equally important, only 21% of subjects had documentation of vitamin D status over the study period. A critical tenant of bone health surveillance is the assessment and optimization of calcium intake and vitamin D status, particularly in individuals who are at nutritional risk. Finally, because many patients with HCU have tall stature, the use of methods to adjust BMD for height should be considered, and a key message of our study is that DXA may overestimate BMD in patients with HCU as well as other disorders characterized by tall stature (e.g. Marfan syndrome). Future research is needed to determine whether height Z-adjusted BMD is a better predictor of fracture than unadjusted BMD in tall individuals. A previous study identified a positive correlation between homocysteine levels and measures of growth including height Z-score and growth velocity, illustrating the point that tall stature should not be assumed to be a marker of health.[25]

In summary, we found that low BMD was a common finding in both adults and pediatric participants with HCU. We believe that our findings, in the context of prior studies, justify routine monitoring of bone health in the HCU population, and should begin in childhood. Regular monitoring of BMD by DXA should be considered and performed according to guidelines issued by the International Society for Clinical Densitometry guidelines.[14] Specifically, in pediatric subjects assessment of BMD should be performed for total body less head and L1-L4 LS; and in adults for LS and hip. Given the early onset of bone deficits

in subjects with HCU, it will be essential to determine the etiology of the adverse skeletal effects in HCU and also to clarify the relationships between HCU treatment, biochemical control, and BMD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

DRW researched data, performed statistical analysis, and wrote the article. J.B. researched the data and wrote the article. KL and CC researched data and reviewed and edited the article. CF, CLF, PK, and MAL contributed to project development, reviewed and edited the article.

Abbreviations

BMC	bone mineral content
BMD	bone mineral density
DXA	dual energy X-ray absorptiometry
HCU	homocystinuria
LS	lumbar spine

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Highlights

- Low bone mineral density was common in homocystinuria (HCU) patients of all ages
- Homocysteine and methionine were positively associated with bone mineral density
- DXA may overestimate bone density in HCU patients with tall stature
- Future studies are needed to clarify the mechanism of low bone density in HCU

Table 1**Participant Characteristics**

	19 Individuals (Baseline Values)	19 Individuals (All values)¹
Male, n	9 (47.4%) ²	9 (47.4%)
Age, yrs	11.5 (3.5 to 49.2) ³	12.8 (3.5 to 51)
Pediatric (< 21 years)	13 (68.4%)	13 (68.4%)
History of fracture ⁴	3 (15.8%)	3 (15.8%)
Height, cm	151.1 (122.9 to 167) ⁵	152.5 (122.9 to 167.6)
Height Z-Score ⁶	0.9 (−0.6 to 0.9) ⁷	0.9 (−0.4 to 1.4) ⁷
Homocysteine, μmol/L	59.2 (38.5 to 152.1) ⁸	105.2 (48.7 to 141.7) ⁹
Methionine, nmol/mL	477.6 (63.8 to 684.4) ⁹	462 (89.8 to 672.5) ¹⁰
Calcium, mmol/L	2.4 (2.3 to 2.5) ¹¹	2.4 (2.3 to 2.5) ¹¹
Calcium, mg/dL	9.7 (9.4 to 9.9) ¹¹	9.6 (9.2 to 9.8) ¹¹
25-hydroxy vitamin D, nmol/L	71.4 (57.4 to 74.1) ¹²	88.9 (80.6 to 95.1) ¹²
25-hydroxy vitamin D, ng/mL	28.6 (23 to 29.7) ¹²	35.6 (32.3 to 38.1) ¹²

¹ averages shown for individuals with >1 value over the study period

² n (%), all such values

³ n (range)

⁴ a total of 5 lifetime fractures occurred in 3 subjects

⁵ n (interquartile range), all such values not otherwise noted

⁶ height Z-scores calculated in individuals 20 years of age using CDC reference data [26]

⁷ available in 13 participants

⁸ available in 15 participants

⁹ available in 16 participants

¹⁰ available in 17 participants

¹¹ available in 14 participants

¹² available in 4 participants

Table 2

DXA Bone Mineral Density and Z-Scores

	19 Individuals ¹ (Baseline Values)	19 Individuals ¹ (All values) ²
Lumbar Spine BMD ³ , g/cm ²	0.666 ± 0.24 ⁴	0.692 ± 0.22
Lumbar Spine BMD Z-score ⁵	-1.2 ± 1.3	-1.14 ± 1.3
Total Hip BMD ⁶ , g/cm ²	0.852 ± 0.08	0.864 ± 0.13
Total Hip BMD ⁷ Z-score	-0.89 ± 0.4	-0.53 ± 0.87
Total Body Less Head BMD ⁸ , g/cm ²	0.683 ± 0.27	0.683 ± 0.27
Total Body Less Head BMD Z-score ⁹	1.05 ± 1.2	1.05 ± 1.2

¹ BMD and Z-scores from clinical reports as determined by manufacturers reference data

² Averages shown for individuals with >1 value over the study period

³ Available in 17 participants

⁴ Median ± SD, all such values

⁵ Available in 18 participants

⁶ Available in 9 participants

⁷ Available in 5 participants

⁸ Available in 4 participants

⁹ Available in 2 participants

Table 3

Correlations between lumbar spine BMD Z-scores and markers of HCU control

	Spearman's rho	P value
First DXA Scan		
Homocysteine (n=13)	0.499	0.08
Methionine (n=14)	0.471	0.08
Average over study period		
Homocysteine (n=17)	0.499	0.05
Methionine (n=17)	0.489	0.05

Table 4

Associations between lumbar spine BMD Z-scores and markers of HCU control by multiple linear regression.

	Beta (95% CI)	P value	R ²
First DXA Scan			
<u>Unadjusted</u>			
Homocysteine ^I (n=13)	0.93 (−0.14,1.99)	0.08	0.26
Methionine ^I (n=14)	1.97 (0.34,3.59)	0.02	0.37
<u>Adjusted for age, sex, & height</u>			
Homocysteine ^I (n=13)	2.11 (1.18,3.05)	0.001	0.79
Methionine ^I (n=14)	2.69 (0.56,4.81)	0.02	0.50
Average over study period			
<u>Unadjusted</u>			
Homocysteine ^I (n=15)	1.67 (−0.06,3.4)	0.06	0.25
Methionine ^I (n=16)	2.31 (0.27,4.35)	0.03	0.30
<u>Adjusted for age, sex, & height</u>			
Homocysteine ^I (n=15)	3.04 (1.35,4.72)	0.01	0.64
Methionine ^I (n=16)	2.89 (0.29,5.49)	0.03	0.40

^I log-transformed