Bone 44 (2009) 954–958

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

Cysteine, homocysteine and bone mineral density: A role for body composition?

Amany K. Elshorbagy [a,*], Clara Gram Gjesdal [b,c], Eha Nurk [d], Grethe S. Tell [b], Per M. Ueland [e,f], Ottar Nygård [g], Aage Tverdal [h], Stein E. Vollset [b,h], A. David Smith [a], Helga Refsum [a,d]

[a] Le Gros Clarke Building, Department of Physiology, Anatomy and Genetics, Oxford University, UK
[b] Department of Public Health and Primary Health Care, University of Bergen, Norway
[c] Department of Rheumatology, Haukeland University Hospital, Bergen, Norway
[d] Institute of Basic Medical Sciences, Department of Nutrition, University of Oslo, Norway
[e] Section of Pharmacology, Institute of Medicine, University of Bergen, Norway
[f] Laboratory of Clinical Biochemistry, Haukeland University Hospital, Norway
[g] Section of Cardiology, Institute of Medicine, University of Bergen and Haukeland University Hospital, Norway
[h] Norwegian Institute of Public Health, Oslo, Norway

ARTICLE INFO

Article history:
Received 17 October 2008
Revised 11 December 2008
Accepted 23 December 2008
Available online 3 January 2009

Edited by: J. Kanis

Keywords:
Homocysteine
Cysteine
BMD
BMI
Fat mass
Lean mass

ABSTRACT

Background: Plasma total cysteine (tCys) and homocysteine (tHcy) are associated with body composition, which in turn affects bone mineral density (BMD).
Objectives: To investigate whether associations of tCys and tHcy with BMD are mediated through body composition (fat mass and/or lean mass).
Design: Using data from 5238 Hordaland Homocysteine Study participants, we fit multiple linear regression models and concentration–response curves to explore the relationships between tCys, tHcy, and BMD, with and without adjustment for body mass index (BMI), lean mass and/or fat mass.
Results: All associations were stronger in women. tCys was positively associated with BMD (women, partial $r=0.11$; men, partial $r=0.07$, $p\leq0.001$ for both), but this association was markedly attenuated after adjustment for fat mass. tHcy showed an inverse association with BMD in women (partial $r=-0.09$, $p<0.001$), which remained significant after adjustment for lean mass and fat mass. In men and women, changes in tCys or tHcy during 6 years were not associated with BMD at follow-up. Weight gain during 6 years predicted higher BMD at follow-up ($p\leq0.009$) independent of nutrient intakes, physical activity and baseline BMI. Baseline tHcy inversely predicted BMD measured 6 years later (partial $r=-0.11$, $p<0.001$ in women; partial $r=-0.07$, $p=0.002$ in men) independent of baseline BMI, while a positive association of baseline tCys with BMD at follow-up (partial $r=0.10$ in women, 0.09 in men, $p\leq0.001$) disappeared after adjustment for baseline BMI.
Conclusion: tHcy is inversely associated with BMD independent of body composition, while the positive association of tCys with BMD appears to be mainly mediated through fat mass.

Introduction

Body total lean mass and fat mass are recognized as key determinants of bone mineral density (BMD) [1], and the WHO has identified low body mass index (BMI) as a risk factor for osteoporosis [2]. We recently reported in a large population-based study that plasma total cysteine (tCys) and to a lesser extent, total homocysteine (tHcy), are important positive and negative predictors respectively of fat mass, assessed by Dual-energy X-ray Absorptiometry (DXA) [3]. One likely mechanism for the striking positive influence of tCys on fat mass is a powerful antilipolytic action of cysteine [4], but other possibilities remain to be explored [3].

This relationship between aminothiols and body composition is consistent with the thin and underweight marfanoid phenotype characterizing cystathionine beta synthase (CBS) deficiency [5–7], in which a transsulfuration block results in a high tHcy and low tCys. Homocystinuria due to CBS deficiency is also characterized by osteoporosis, which occurs in 50–70% of cases by age 20 years [8], and has hitherto mainly been attributed to hyperhomocysteinemia. The possible role for decreased tCys in osteoporosis of CBS deficiency warrants further investigation, as osteoporosis has not been reported in other genetic homocystinurias in which cysteine synthesis is normal [9].

A recent study in postmenopausal women reported a strong association between decreased tCys and osteoporosis [10]. The authors proposed that this may be due to either reduced availability of cysteine for collagen formation, or increased cysteine utilization by

* Corresponding author. Fax: +44 1865285813.
E-mail address: amany.elshorbagy@dpag.ox.ac.uk (A.K. Elshorbagy).

8756-3282/$ – see front matter © 2009 Elsevier Inc. All rights reserved.
doi:10.1016/j.bone.2008.12.018

proteases in the osteoclastic hyper-activity underlying the osteoporotic process. In the present study we sought to investigate a third possibility, namely whether any effects of tCys and/or tHcy on BMD are mediated through their influence on body fat mass, a recognized determinant of BMD [1].

Subjects and methods

Study population

The first Hordaland Homocysteine Study (HHS-I) was conducted in 1992–1993, on 18043 40–67 year-old residents of Hordaland county of Western Norway. In a follow-up study in 1997–1999 (HHS-II), 9187 subjects were re-invited as part of the Hordaland Health Study (HUSK); 7074 (77%) attended. Details of recruitment, outcomes and ethical approval for both studies have been reported before [11].

This study is based on data from 3009 women and 2229 men who participated in both HHS-1 (baseline) and HHS-II (follow-up). Selection was based on availability of data on tCys, tHcy, weight and height at both time-points, and lean mass, fat mass and BMD at follow-up (HHS-II). Of these participants, 1237 men and 1867 women were aged 40–42 y in 1992, while 992 men and 1142 women were aged 65–67 y.

Study variables

Anthropometry and body composition

Height and weight were measured in light clothing, to the nearest 1 cm and 0.5 kg respectively, and BMI was calculated. Total body lean mass, fat mass, and total body BMD were measured using DXA [12]. Principles and details of DXA measurements in HHS-II have been described previously [13].

Lifestyle and dietary data

Self-administered questionnaires provided information on diet [14] (HHS-II only) and lifestyle (HHS-I and II). Nutrient and total energy intakes were calculated using a software system developed at the Department of Nutrition, University of Oslo, and analyzed in this study as continuous variables. Physical activity in HHS-II included 2 variables indicating heavy or light physical activity in the past year, with 4 duration categories within each variable, while in HHS-I it comprised 4 strenuousness categories. Smoking (HHS-I) and coffee consumption variables indicated the number of cigarettes or cups consumed per day. Smoking habits in HHS-II were categorized as 1—never-smoker, 2—ex-smoker, 3—pipe/cigar-smoker, 4—non-daily cigarette smoker and 5—daily cigarette smoker.

Biochemical measurements

Non-fasting plasma samples were collected in EDTA-containing tubes for tCys and tHcy analyses, which were performed using HPLC with fluorescence detection. Intra-assay coefficient of variation was lower than 4% [15]. Creatinine (HHS-II only) was measured in stored plasma using a modification of a liquid chromatography–mass spectrometry (LC–MS/MS) described previously [16].

Statistical methods

Skewed variables, namely tHcy and creatinine were log-transformed prior to regression analysis. Groups were compared by Mann–Whitney *U* test for gender differences and Wilcoxon signed rank test for paired differences between baseline and follow-up. Owing to previously reported gender differences in the relationship of tHcy [17] and body composition [1] with BMD, all analyses were performed separately in men and women and, in correlation and regression analyses, adjusted for age.

Age-adjusted Pearson correlation coefficients investigated simple correlations among the sulfur aminoacids, BMD, and anthropometric parameters. Multiple linear regression models were then used to assess the role of body composition as a mediator in the cross-sectional associations of tCys and tHcy with BMD. BMD was always entered as the dependent variable, with age, tCys and tHcy simultaneously as predictor variables. Various models were additionally adjusted for lean mass and/or fat mass with or without other factors selected by the strength of simple Pearson correlations or with suspected biological influence on BMD.

We similarly investigated whether baseline values or changes in tCys and tHcy were associated with BMD at follow-up (6 years later) by linear regression, and whether body weight acts as a mediator in these associations. Since body composition was not measured at baseline, these linear regression models were adjusted for relevant BMI variables.

To reveal non-linear relationships, concentration–response curves were constructed to show the estimated difference in BMD by tCys and tHcy, with and without adjustment for BMI or total lean mass and fat mass. We used Gaussian generalized additive regression models, as implemented in S-PLUS 6.2 for Windows (Insightful Corporation, Seattle, WA). On the *y*-axis, the model generates a reference value of zero corresponding to the approximate value of BMD associated with the mean tCys or tHcy for all subjects. Corresponding partial correlation coefficients and *p*-values were obtained from multiple linear regression analyses. Because patterns were similar both for cross-sectional and longitudinal associations, only the plots of baseline aminothiols vs. BMD at follow-up are shown.

Apart from the concentration–response curves, all analyses were performed using the Statistical Package for Social Sciences 12.0 for Windows (SPSS, Chicago. IL). p-values<0.05 were considered significant.

Results

Population characteristics relevant to this study are shown in Table 1. Men had significantly lower fat mass but had higher tHcy, tCys, lean mass and total body BMD than women ($p<0.001$). Follow-up concentrations of tCys were significantly higher than baseline values in both genders ($p<0.001$). 27% of men and 29% of women smoked cigarettes daily at baseline, compared to 22% of men and 25% of women at follow-up.

Simple age-adjusted Pearson correlations of the baseline and follow-up concentrations of aminothiols, with BMD and anthro-

Table 1
Population distribution for selected parameters at follow-up[1]

		Men $N=2229$	Women $N=3009$
BMI, kg/m^2	*Baseline*	25.1 (21.1, 30.7)[a]	23.9 (19.6, 31.4)[a]
	Follow-up	25.9 (21.3, 31.7)	24.7 (19.9, 33.1)
Lean mass, kg		57.6 (47.2, 68.9)	39.1 (32.1, 47.4)
Fat mass, kg		19.9 (8.6, 36.3)	24.0 (12.6, 42.8)
Total body BMD, g/cm^2		1.192 (1.035, 1.346)	1.133 (0.911, 1.281)
tCys[b], μmol/L	*Baseline*	282 (232, 342)[a]	265 (215, 334)[a]
	Follow-up	295 (242, 363)	282 (226, 362)
tHcy, μmol/L	*Baseline*	11.0 (7.8, 17.5)	9.4 (6.3, 15.9)
	Follow-up	11.0 (7.6, 18.3)	9.3 (6.2, 16.2)
Creatinine, μmol/L		80 (61, 108)	65 (49, 87)
Vitamin D intake μg/d		8.4 (2.5, 30.0)	6.1 (1.4, 25.9)
Calcium intake, mg/d		828 (375,1545)	707 (298, 1332)

[1]Unless otherwise noted. Data presented as median (5th–95th percentiles). All parameters are significantly different in men vs. women by Mann–Whitney *U* test.
[a] Significantly different compared to follow-up within the same gender by Wilcoxon signed rank test.
[b] tCys, plasma total cysteine; tHcy, plasma total homocysteine.

Table 2
Simple Pearson correlations of tCys and tHcy with BMD and anthropometric parameters measured at follow-up[1,2]

		Lean mass	Fat mass	Weight	Height	BMI	BMD
Men (N=2192)							
Log tHcy	*Baseline*	0.01	0.06*	0.05*	0.03	0.04	−0.04
	Follow-up	0.04*	0.05*	0.06*	0.03	0.05*	0.00
tCys	*Baseline*	0.07*	0.21**	0.19**	0.02	0.20**	0.07**
	Follow-up	0.08**	0.24**	0.21**	0.02	0.23**	0.06*
BMD	*Follow-up*	0.41**	0.18**	0.37**	0.23**	0.29**	
Women (N=2975)							
Log tHcy	*Baseline*	−0.01	0.04*	0.03	0.01	0.03	−0.08**
	Follow-up	−0.01	0.05*	0.04*	0.01	0.03	−0.06*
tCys	*Baseline*	0.13**	0.24**	0.24**	0.02	0.25**	0.07**
	Follow-up	0.14**	0.30**	0.29**	0.02	0.30**	0.08**
BMD	*Follow-up*	0.35**	0.24**	0.34**	0.19**	0.28**	–

[1]tCys, plasma total cysteine; tHcy, plasma total homocysteine; BMD, bone mineral density.
[2]Correlation coefficients are adjusted for age-group and are marked by * for $p<0.05$ and ** for $p<0.001$.

pometric parameters measured at follow-up are shown in Table 2. As expected, BMD showed strong positive correlations with lean mass, weight, height and BMI, and to a slightly lesser extent with fat mass. Baseline and follow-up concentrations of tCys correlated positively with fat mass and BMD in men and women. tHcy at baseline and follow-up was inversely associated with BMD in women. Neither tCys nor tHcy were associated with height.

The apparent positive associations of tHcy with body weight parameters are largely explained through the association of tHcy with tCys [3], since tHcy is known to correlate inversely with these measures in multivariate analysis adjusted for tCys [3]. Similarly, the apparent correlations of tCys with lean mass have been shown previously to disappear after adjustment for fat mass [3].

In summary, tCys correlates positively with fat mass and BMD, while tHcy tends to correlate negatively with these parameters. Since tCys and tHcy are tightly linked [3], and have opposite effects on the outcome variable of interest (BMD; Table 2), the multivariate linear regression analyses below are always reciprocally adjusted for tCys or tHcy.

Body composition as a possible mediator in the cross-sectional associations of tCys and tHcy with BMD at follow-up

Table 3 shows the effect of adjustment for different anthropometric parameters on the age-adjusted associations of tCys and tHcy with BMD (as outcome variable) in a linear regression model. Similar to previous findings for total hip BMD in the same population [17], tHcy was not a significant predictor of total body BMD in men, while in women, it showed an inverse association with BMD, after controlling for age and tCys. This association remained robust after adjustment for lean mass and fat mass (Table 3), and with further adjustment for height, diet (intakes of calcium, vitamin D, protein, and coffee), plasma creatinine, smoking habits and physical activity (partial $r=-0.09$, $p<0.001$).

Controlling for age and tHcy, tCys was positively associated with BMD in both men (partial $r=0.07$, $p=0.001$) and women (partial $r=0.11$, $p<0.001$), but these associations were abolished by adjusting for lean mass and fat mass. When tested separately, it was fat mass rather than lean mass that markedly weakened the association of tCys with BMD (Table 3). When fat mass and lean mass were excluded from the model, adjusting for height and intakes of calcium, vitamin D, protein, and coffee, as well as smoking habits, physical activity and plasma creatinine, had minor effects on the association of tCys with BMD in men (partial r for tCys $=0.06$, $p=0.018$) and women (partial r for tCys $=0.09$, $p<0.001$).

Effect of changes in tCys, tHcy and BMI during 6 years on BMD at follow-up

Changes in tCys and tHcy were not associated with BMD at follow-up in a multiple linear regression model adjusted for age, baseline BMI and changes in BMI. Baseline BMI was a powerful positive predictor of BMD in the same model (partial $r=0.30$ and 0.28 in men and women respectively, $p<0.001$ for both). Change in BMI over 6 years also correlated directly with BMD (partial $r=0.06$, $p=0.009$ in men and partial $r=0.07$, $p<0.001$ in women) despite adjustment for baseline BMI; i.e. weight gain was associated with higher BMD and weight loss predicted a lower BMD at follow-up independent of initial body weight and changes in tCys and tHcy.

BMI as a possible mediator in the associations of tCys and tHcy at baseline with BMD at follow-up

Fig. 1 shows significant positive and negative associations respectively, of baseline tCys and tHcy, with BMD at follow-up in both men and women, with reciprocal adjustment for tCys or tHcy. After controlling for baseline BMI, only the tHcy associations persisted while the tCys associations became non-significant. Conversely, baseline BMI showed strong associations with follow-up BMD (partial $r=0.29$ in men, and partial $r=0.28$ in women, $p<0.001$ for both), that were not attenuated after adjustment for tCys (data not shown).

In both men and women, the relationship of baseline tHcy with follow-up BMD was stronger than the cross-sectional association at follow-up. The prospective negative tHcy-BMD association was virtually unchanged after adjustment for smoking habits, coffee consumption, and physical activity at baseline as well as plasma creatinine and dietary intakes of calcium, vitamin D, and protein at follow-up (partial r for tHcy $=-0.09$, $p=0.002$ in women, partial $r=-0.08$, $p=0.003$ in men).

In summary, tCys at baseline and follow-up showed positive associations with BMD that were markedly weakened or abolished after adjustment for fat mass or BMI. In contrast, the negative association of tHcy with BMD persisted after controlling for fat mass or BMI.

Discussion

We investigated the role of body mass and composition as mediators in the associations of tCys and tHcy with BMD. We report

Table 3
Effect of adjustment for body weight and composition on cross-sectional age-adjusted partial correlation coefficients of tCys and tHcy with total body BMD[a]

Model (additional covariates)[b]	Men		Women	
	tCys	Log tHcy	tCys	Log tHcy
1	0.07	−0.02	0.11	−0.09
	(*p=0.001*)	(*p=0.29*)	(*p<0.001*)	(*p<0.001*)
2 (lean mass)	0.04	−0.03	0.06	−0.08
	(*p=0.078*)	(*p=0.21*)	(*p=0.001*)	(*p<0.001*)
3 (fat mass)	0.02	−0.01	0.04	−0.08
	(*p=0.29*)	(*p=0.55*)	(*p=0.041*)	(*p<0.001*)
4 (lean mass and fat mass)	0.03	−0.03	0.03	−0.07
	(*p=0.23*)	(*p=0.24*)	(*p=0.086*)	(*p<0.001*)
5 (BMI)	0.00	−0.01	0.02	−0.07
	(*p=0.82*)	(*p=0.50*)	(*p=0.23*)	(*p<0.001*)
6 (body weight)	*−0.01* (*p=0.70*)	−0.02	0.01	−0.07
		(*p=0.36*)	(*p=0.69*)	(*p<0.001*)

[a] At follow-up, using linear regression with BMD as outcome variable. tCys, plasma total cysteine; tHcy, plasma total homocysteine; BMD, bone mineral density. $N=2229$ men and 3009 women.
[b] All models simultaneously include age, tCys and log tHcy as independent variables, and are adjusted for different anthropometric measures as indicated.

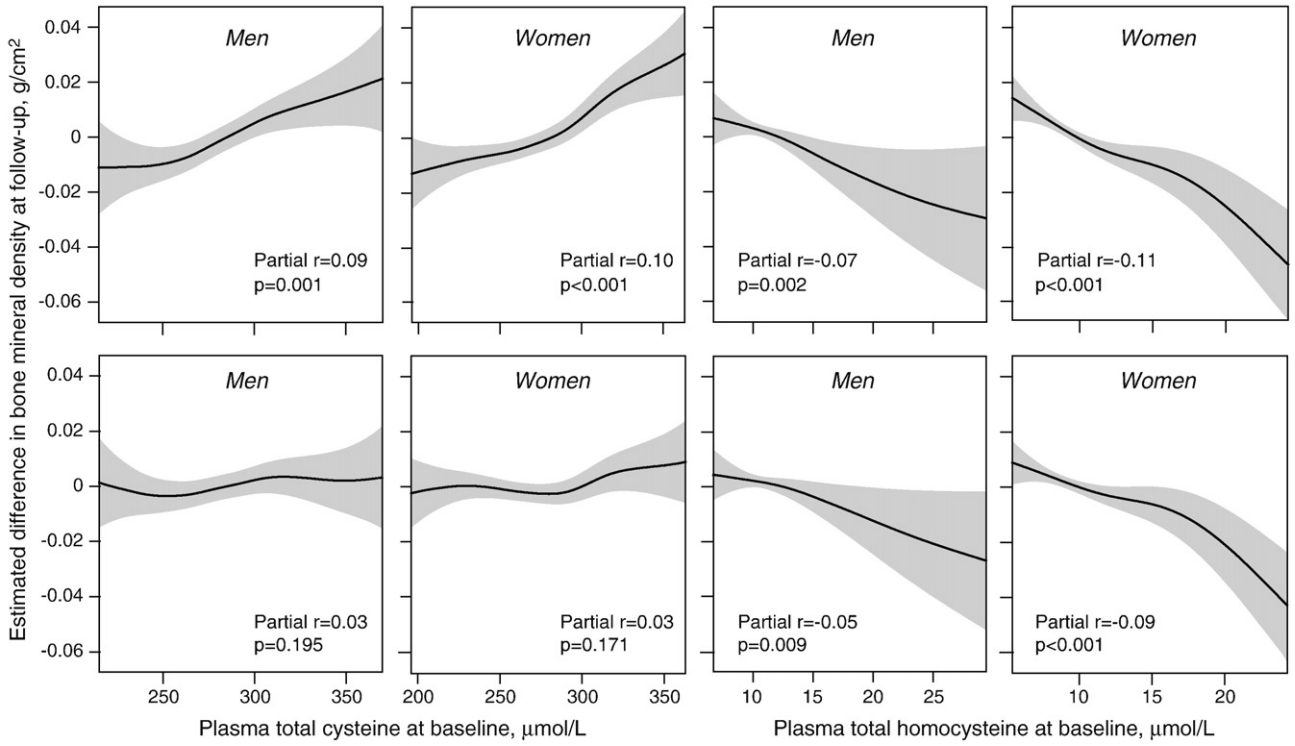

Fig. 1. Concentration–response curves (solid lines) with 95% confidence intervals (shaded areas) for associations of baseline plasma total homocysteine (tHcy) and cysteine (tCys) with bone mineral density (BMD) measured 6 years later. $N = 2229$ men and 3009 women. Upper panel curves are adjusted for age and reciprocally adjusted for tCys or tHcy. Lower panel curves are additionally adjusted for baseline BMI. The reference value ($=0$) of BMD is the value associated with the mean tCys or tHcy for all subjects. Curves were fitted by Gaussian generalized additive regression models while *p*-values and partial correlation coefficients were obtained from corresponding linear regression analyses. The lowest and highest 1 percentile of independent variables are not shown.

for the first time a prospective association of tCys with BMD measured 6 years later. However, our cross-sectional and prospective data suggest that tCys is a positive predictor of BMD only in so far as it predicts a higher body weight. Conversely, the negative association of tHcy with BMD in the present study was independent of body mass and composition.

We previously reported in HHS that the negative impact of tHcy on total hip BMD was significant only in women [17]; the same was observed in the present study using total body BMD. However, in the present study, the prospective association of tHcy at baseline with BMD measured 6 years later was stronger than the cross-sectional associations and was also significant in men. Other studies investigating this issue simultaneously in men and women either found no gender difference or that the relationship was stronger in men (epidemiologic studies and possible pathophysiologic mechanisms reviewed in [18]). That the baseline tHcy concentrations were stronger predictors of BMD than follow-up concentrations may point to the slow and long-standing nature of homocysteine-related pathology. This is evidenced also by our observation that 6-year changes in tHcy were not associated with BMD at follow-up when baseline concentrations were taken into account. Consistent with this, several homocysteine-lowering trials with relatively short durations (1–2 years) failed to document an improvement in bone turnover markers or BMD [19,20].

The tCys-BMD association in our dataset, largely mediated via body fat mass, was stronger in women, consistent with stronger tCys-fat mass [3] and fat mass-BMD [1] associations in women. Conversely, the tCys-BMD association reported by Baines et al. [10] in 328 post-menopausal women remained significant after adjustment for body weight, a discrepancy that may be partly related to their use of BMD measured at the os calcis, versus the total body BMD measurements used in the present study. Moreover, in their analysis of the non-smoking subgroup of 271 women, the association of tCys with BMD was non-significant after controlling for body weight, though we did not observe a similar interaction with smoking in our dataset.

Taking into account the accumulating evidence pointing to tCys as a causal determinant of increased body weight [21], our findings can be interpreted in the context of fat mass being on the causal pathway from tCys to BMD. At least two non-mutually-exclusive mechanisms are currently recognized which explain the relationship of fat mass with BMD. One mechanism involves the mechanical effect of weight-related gravitational forces in increasing bone density. Alternatively, or additionally, recent reviews on fat–bone relationships discuss various cytokines and hormones that may provide the chemical signal by which a higher body weight promotes a protective increase in bone density [22,23]. One such candidate, though not mentioned in these reviews, is of particular relevance here, as it is up-regulated in adipose tissue hyperplasia and adipogenesis [24], positively correlates with both BMI [25] and BMD [26], and is rich in cysteine. This is the matricellular glycoprotein osteonectin, also known as secreted protein, acidic and rich in cysteine (SPARC).

Although it is uncertain how far plasma cysteine availability can limit SPARC secretion, cysteine is known to limit the synthesis of glutathione, a vital antioxidant containing one cysteine residue per molecule [27,28]. It is thus plausible that SPARC synthesis may be positively influenced by tCys concentrations, thus simultaneously promoting fat deposition and bone thickening. We hypothesize that SPARC secretion may be decreased in CBS-deficient homocystinuria patients with decreased tCys, thus contributing to the combination of thinness and osteoporosis observed in these patients. Yet this is unlikely to be the only mechanism involved, and it remains possible that other factors may link cysteine to bone health independent of adiposity.

In summary, we have demonstrated that previously reported negative correlations of tHcy with BMD are independent of body

composition, while tCys positively correlates with BMD mainly through its influence on body fat mass. We propose osteonectin as a potential link between cysteine availability, fat deposition and bone density that warrants further investigation. One practical implication of the present study and that by Baines et al. [10], is that cysteine deficiency may be more relevant to the pathogenesis of osteoporosis in CBS deficient-homocystinuria than is currently believed. This would support the rationale of treatment strategies involving cysteine supplementation in homocystinuria, which are "accepted but not widely used" [29]. However, further work is required to establish to what extent osteoporosis in these patients correlates with the negative impact of low cysteine on their body weight.

Acknowledgments

Amany Elshorbagy is in receipt of an Egyptian Government scholarship fund. This study has also received support from the Advanced Research Programme of Norway, The Norwegian Research Council, The Johan Throne Holst Foundation for Nutrition Research, University of Oslo, and the Foundation to promote research into functional B12-deficiency, Norway. None of the funding bodies were involved in the study design; collection, analysis, or interpretation of the data; or preparation of the manuscript.

Author contributions

Elshorbagy: Concept, design, statistical analysis and interpretation, preparation of first draft.

Gjesdal: Data collection, critical revision of the manuscript.

Nurk: Interpretation and critical revision of the manuscript.

Tell: Planning, design, conduct and data collection of the Hordaland Health Study (HUSK) and the HHS II. Interpretation, comments and critical revisions of the manuscript drafts.

Ueland: Data collection, critical revision of the manuscript.

Nygård: Data collection of HHS-I, critical revision of the manuscript.

Tverdal: Data collection and critical revision of the manuscript.

Vollset: Data collection, critical revision of the manuscript.

Smith: Critical revision of the manuscript.

Refsum: Concept, design, data collection, analysis, critical revision of the manuscript.

References

[1] Gjesdal CG, Halse JI, Eide GE, Brun JG, Tell GS. Impact of lean mass and fat mass on bone mineral density: the Hordaland Health Study. Maturitas 2008;59:191–200.
[2] Prevention and management of osteoporosis. World Health Organ Tech Rep Ser 2003;921:1–164, back cover.
[3] Elshorbagy AK, Nurk E, Gjesdal CG, et al. omocysteine, cysteine, and body composition in the Hordaland Homocysteine Study: does cysteine link amino acid and lipid metabolism? Am J Clin Nutr 2008;88:738–46.
[4] Olefsky JM. Comparison of the effects of insulin and insulin-like agents on different aspects of adipocyte metabolism. Horm Metab Res 1979;11:209–13.
[5] Mudd SH, Levy HL, Skovby F. Disorders of transsulfuration. In: Scriver CR, Beaudet AL, Sly WS, Valle D, editors. The molecular and metabolic bases of inherited disease. 7th ed. New York: McGraw-Hill; 1995. p. 1279–327.
[6] Kaur M, Kabra M, Das GP, Suri M, Verma IC. Clinical and biochemical studies in homocystinuria. Indian Pediatr 1995;32:1067–75.
[7] Brenton DP, Dow CJ, James JI, Hay RL, Wynne-Davies R. Homocystinuria and Marfan's syndrome. A comparison. J Bone Jt Surg Br 1972;54:277–98.
[8] Mudd SH, Skovby F, Levy HL, et al. The natural history of homocystinuria due to cystathionine beta-synthase deficiency. Am J Hum Genet 1985;37:1–31.
[9] Kraus JP, Kožich V. Cystathionine β synthase and its deficiency. In: Carmel R, Jacobsen DW, editors. Homocysteine in health and disease. First ed. Cambridge: Cambridge University Press; 2001. p. 223–44.
[10] Baines M, Kredan MB, Davison A, et al. The association between cysteine, bone turnover, and low bone mass. Calcif Tissue Int 2007;81:450–4.
[11] Refsum H, Nurk E, Smith AD, et al. The Hordaland Homocysteine Study: a community-based study of homocysteine, its determinants, and associations with disease. J Nutr 2006;136:1731S–40S.
[12] Pietrobelli A, Formica C, Wang Z, Heymsfield SB. Dual-energy X-ray absorptiometry body composition model: review of physical concepts. Am J Physiol 1996;271:E941–51.
[13] Gjesdal CG, Aanderud SJ, Haga HJ, Brun JG, Tell GS. Femoral and whole-body bone mineral density in middle-aged and older Norwegian men and women: suitability of the reference values. Osteoporos Int 2004;15:525–34.
[14] Andersen LF, Nes M, Lillegaard IT, Sandstad B, Bjorneboe GE, Drevon CA. Evaluation of a quantitative food frequency questionnaire used in a group of Norwegian adolescents. Eur J Clin Nutr 1995;49:543–54.
[15] Fiskerstrand T, Refsum H, Kvalheim G, Ueland PM. Homocysteine and other thiols in plasma and urine: automated determination and sample stability. Clin Chem 1993;39:263–71.
[16] Holm PI, Ueland PM, Kvalheim G, Lien EA. Determination of choline, betaine, and dimethylglycine in plasma by a high-throughput method based on normal-phase chromatography–tandem mass spectrometry. Clin Chem 2003;49:286–94.
[17] Gjesdal CG, Vollset SE, Ueland PM, et al. Plasma total homocysteine level and bone mineral density: the Hordaland Homocysteine Study. Arch Intern Med 2006;166:88–94.
[18] Herrmann M, Peter Schmidt J, Umanskaya N, et al. The role of hyperhomocysteinemia as well as folate, vitamin B(6) and B(12) deficiencies in osteoporosis: a systematic review. Clin Chem Lab Med 2007;45:1621–32.
[19] Herrmann M, Umanskaya N, Traber L, et al. The effect of B-vitamins on biochemical bone turnover markers and bone mineral density in osteoporotic patients: a 1-year double blind placebo controlled trial. Clin Chem Lab Med 2007;45:1785–92.
[20] Green TJ, McMahon JA, Skeaff CM, Williams SM, Whiting SJ. Lowering homocysteine with B vitamins has no effect on biomarkers of bone turnover in older persons: a 2-y randomized controlled trial. Am J Clin Nutr 2007;85:460–4.
[21] Elshorbagy AK, Refsum H, Smith AD, Graham IM. The association of cysteine and gamma-glutamyl transferase with BMI and obesity. Obesity in press.
[22] Zhao LJ, Jiang H, Papasian CJ, et al. Correlation of obesity and osteoporosis: effect of fat mass on the determination of osteoporosis. J Bone Miner Res 2008;23:17–29.
[23] Reid IR. Relationships between fat and bone. Osteoporos Int 2008;19:595–606.
[24] Chavey C, Boucher J, Monthouel-Kartmann MN, et al. Regulation of secreted protein acidic and rich in cysteine during adipose conversion and adipose tissue hyperplasia. Obesity (Silver Spring) 2006;14:1890–7.
[25] Takahashi M, Nagaretani H, Funahashi T, et al. The expression of SPARC in adipose tissue and its increased plasma concentration in patients with coronary artery disease. Obes Res 2001;9:388–93.
[26] Mansergh FC, Wells T, Elford C, et al. Osteopenia in Sparc (osteonectin)-deficient mice: characterization of phenotypic determinants of femoral strength and changes in gene expression. Physiol Genomics 2007;32:64–73.
[27] Glazenburg EJ, Jekel-Halsema IM, Scholtens E, Baars AJ, Mulder GJ. Effects of variation in the dietary supply of cysteine and methionine on liver concentration of glutathione and "active sulfate" (PAPS) and serum levels of sulfate, cystine, methionine and taurine: relation to the metabolism of acetaminophen. J Nutr 1983;113:1363–73.
[28] Stipanuk MH, Dominy Jr JE, Lee JI, Coloso RM. Mammalian cysteine metabolism: new insights into regulation of cysteine metabolism. J Nutr 2006;136:1652S–9S.
[29] Lee PJ, Briddon A. A rationale for cystine supplementation in severe homocystinuria. J Inherit Metab Dis 2007;30:35–8.