Bone 108 (2018) 20–24

Contents lists available at ScienceDirect

Bone

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

Full Length Article

Sex hormones are negatively associated with vertebral bone marrow fat

Swaroop D. Mistry [a,*], Gina N. Woods [b], Sigurdur Sigurdsson [c], Susan K. Ewing [a], Trisha F. Hue [a], Gudny Eiriksdottir [c], Kaipin Xu [d], Joan F. Hilton [a], Deborah M. Kado [e], Vilmundur Gudnason [c], Tamara B. Harris [g], Clifford J. Rosen [f], Thomas F. Lang [d], Xiaojuan Li [d], Ann V. Schwartz [a]

[a] Department of Epidemiology and Biostatistics, University of California San Francisco, CA 94158, USA
[b] Department of Medicine, University of California San Diego, CA 92093, USA
[c] Icelandic Heart Association Research Institute, Iceland
[d] Department of Radiology and Biomedical Imaging, University of California San Francisco, CA 94107, USA
[e] Department of Family Medicine and Family Health, University of California San Diego, CA 92093, USA
[f] Maine Medical Center Research Institute, Portland, ME 04102, USA
[g] Intramural Research Program, National Institute of Aging, 20892, USA

A R T I C L E I N F O

Article history:
Received 26 June 2017
Revised 8 December 2017
Accepted 10 December 2017
Available online 11 December 2017

Keywords:
Sex hormones
Estradiol
Testosterone
Vertebral bone marrow fat

A B S T R A C T

Context: Higher bone marrow fat (BMF)[1] is associated with osteoporosis and reduced hematopoiesis. Exogenous estradiol reduces BMF in older women, but effects of endogenous sex hormones are unknown.
Objective: To determine if endogenous sex hormones are associated with BMF in older men and women.
Design, setting and participants: Cross-sectional study in the Age Gene/Environment Susceptibility (AGES) Reykjavik cohort. Participants using medications that may affect BMF were excluded.
Main outcome measures: Vertebral BMF was measured with magnetic resonance spectroscopy. Estradiol, testosterone and sex hormone binding globulin were measured on archived serum. Linear regression models were adjusted for age, total percent body fat and visit window.
Results: Analyses included 244 men and 226 women, mean age 81.5 (SD 4.1) years. Mean BMF was 54.1% (SD 8.6) (men) and 54.7% (SD 8.1) (women). In adjusted models, per 1 pg/ml increase in total estradiol, there was a statistically significant 0.26% decrease in BMF in men (95% CI: −0.41, −0.11) and a non-significant 0.20% decrease in women (95% CI: −0.55, 0.15), with no evidence of interaction by gender ($p = 0.88$). Per 10 ng/dl increase in total testosterone, there was a significant 0.10% decrease in BMF in men (95% CI: −0.17, −0.03) and a non-significant 0.13% (95% CI: −0.79, 0.53) decrease in women, with no evidence of interaction by gender ($p = 0.97$).
Conclusion: Higher bone marrow fat is associated with lower total estradiol and testosterone levels in older men, with a similar but statistically non-significant association in older women. Sex hormone levels appear to play a role in the regulation of bone marrow fat in older adults.

© 2017 Elsevier Inc. All rights reserved.

1. Introduction

Humans have little marrow fat at birth, but marrow adiposity increases with age, particularly during the third decade of life. Marrow fat in postmortem iliac crest bone biopsies increased from 40% at age 30 to 68% by age 100 years. Both the size and number of adipocytes appear to increase with age [1]. While these changes in bone marrow fat (BMF) have been recognized for years, appreciation of its role and functions has been a recent development. BMF may be an important determinant of skeletal health. Observational studies have shown that higher BMF is associated with lower bone density and with prevalent vertebral fractures, including our investigation of these associations in the Iceland Age Gene/Environment Susceptibility (AGES) Reykjavik cohort [2,3]. BMF may also affect hematopoiesis and stem cell function [4]. Given the emerging evidence implicating marrow fat as an important factor involved in the regulation of both bone and stem cell function, better understanding of the mechanisms underlying marrow fat accumulation is essential.

Sex hormone levels may play an important regulatory role for marrow fat. Further, since total sex hormone levels differ by gender, dependence of BMF on sex hormones also might differ by gender. In rodents, ovariectomy increases BMF [5]. Estrogen administration prevents this increase in BMF [6]. Clinical trials in older women have demonstrated

* Corresponding author at: 1500 Owens Street, Suite 300 San Francisco, CA 94158, USA.
E-mail addresses: Swaroop.Mistry@ucsf.edu (S.D. Mistry), gwoods@ucsd.edu (G.N. Woods), sigurdur@hjarta.is (S. Sigurdsson), sewing@psg.ucsf.edu (S.K. Ewing), thue@psg.ucsf.edu (T.F. Hue), gudny@hjarta.is (G. Eiriksdottir), Kaipin.Xu@ucsf.edu (K. Xu), Joan.Hilton@ucsf.edu (J.F. Hilton), dkado@ucsd.edu (D.M. Kado), villi@hjarta.is (V. Gudnason), Harris99@nia.nih.gov (T.B. Harris), cjrofen@gmail.com (C.J. Rosen), Thomas.Lang@ucsf.edu (T.F. Lang), Xiaojuan.Li@ucsf.edu (X. Li), aschwartz@psg.ucsf.edu (A.V. Schwartz).

[1] BMF, Bone Marrow Fat

https://doi.org/10.1016/j.bone.2017.12.009
8756-3282/© 2017 Elsevier Inc. All rights reserved.

that exogenous estrogen reduces age-related increases in BMF [7,8]. However, there are no studies to date of the effect of endogenous estrogen levels on marrow fat in humans. In addition, studies are not available on the relationship between testosterone levels and BMF. The objective of this study is to investigate the cross-sectional associations between endogenous sex hormone concentrations and vertebral marrow fat in older men and women, using data from the AGES-Reykjavik cohort.

2. Subjects and methods

2.1. Study population

This is a cross sectional ancillary study in the AGES-Reykjavik cohort. AGES-Reykjavik, a population-based study of older men and women in Iceland, was designed to examine the genetic susceptibility and gene/environment interactions contributing to phenotypes of old age [9]. The first AGES-Reykjavik visit, conducted in 2002 to 2006, included 5764 men and women aged 67 to 93. In 2007–2011, 3411 participants returned for a second visit. At this 2nd AGES visit, bone marrow fat was measured in 301 participants in 2010–2011. In 2015, an additional 238 participants from the cohort of 3411 participants seen at the second AGES visit had BMF measured. In 2016, estradiol, testosterone, and sex hormone binding globulin (SHBG) were measured on archived serum from participants who had BMF measured. Two participants did not have acceptable serum specimens. Participants were excluded ($N = 66$) who reported current use of medications that might affect bone marrow fat, including thiazolidinediones, oral glucocorticoids, treatments for osteoporosis (bisphosphonates, raloxifene, calcitonin, or parathyroid hormone), hormone therapy, tibolone, antiepileptics, and aromatase inhibitor therapy). One participant was excluded due to very high estradiol and testosterone levels. There were 470 participants with sex hormone levels available for these analyses.

The ancillary study was approved by the institutional review boards of the National Bioethics committee in Iceland, the National Institute of Aging, and the University of California, San Francisco (UCSF). All participants provided written informed consent.

2.2. Outcome variable: Vertebral bone marrow fat

Participants attended a clinic visit that included measurement of BMF, whole body composition by DXA and a blood draw. Vertebral BMF was measured with a 1.5-T scanner (GE Healthcare, Milwaukee, Wisconsin) with an 8-channel cervical-thoracic-lumbar-spine coil (using the lower 3 elements; GE Healthcare). Single voxel MRS was acquired in individual vertebral bodies from L1–L4 using single voxel proton magnetic resonance spectroscopy (^{1}H-MRS) based on point resolved spectroscopy (PRESS) sequence. The PRESS box was positioned in the middle of the vertebral body and the PRESS box size was kept the same for each vertebral level for all subjects. Two peaks were quantified: water around 4.65 ppm and bulk methylene protons (saturated lipids) around 1.3 ppm. Vertebral BMF is a ratio of fat to water plus fat, measured as a percentage. For the main analyses, an average BMF for the four vertebral levels (L1–L4) was calculated. The imaging center at AGES-Reykjavik used highly stringent and reproducible daily quality assurance tests based on GE's System Performance Test (SPT). Weekly stability and calibration tests were performed.

2.3. Exposure variables: Estradiol, testosterone, and SHBG levels

Blood was drawn fasting within 2 weeks of the BMF visit. Serum was stored at −80 °C. Sex hormones were measured on the archived serum in January 2016 in one batch (Endoceutics Clinique, Quebec, Canada). Total estradiol and total testosterone were analyzed using gas chromatography/mass spectrometry (Shimadzu Nexera/Qtrap 6500) [10]. The lower limits of quantification for estradiol and testosterone were 1 pg/ml and 50 pg/ml. The inter-assay CV (%) at the LLOQ were 4.7 and 3.6 pg/ml for estradiol and testosterone. Values were extrapolated below the LLOQ using Analyst software (AB Sciex, Concord, Canada). GC/MS provides the most accurate readings in participants with low levels of estradiol and testosterone. Free estradiol and free testosterone were calculated using the Mazer eq. [11]. SHBG was measured using ELISA (Asbach Medical Products) with inter-assay variations (CV %) of 7.7% and 8.8% at 15.995 nmol/l and 179.410 nmol/l respectively.

2.4. Covariates

Participants in the ancillary study also had DXA scans of the whole body, hip and spine. Scans were obtained with a GE Healthcare Lunar iDXA scanner, software version 11.4. Models were adjusted for total fat from DXA whole body scans since total fat influences levels of sex hormones and may influence BMF. Although hip and spine BMD are available for these participants, models were not adjusted for BMD. BMD is associated with marrow fat in this cohort [2] and is known to be associated with sex hormone levels [12]. However, BMD was not included as a covariate in adjusted models because it is not a confounder (i.e., a cause of sex hormone levels and marrow fat), but is rather an effect of these variables. Adjusting for an effect of exposure and outcome may introduce "collider" bias [13]. Because participants were seen for bone marrow fat measurements in two windows of time, 2010–2011 and 2015, the models were adjusted for visit window. Models were also adjusted for age at time of BMF measurement. Analysis was stratified by gender because of the large differences between older men and women in the levels of estradiol and testosterone.

2.5. Statistical methods

Baseline characteristics of participants were summarized using means and standard deviations (SD). Scatterplots of sex hormones versus BMF and Pearson's correlations were run separately for men and women. Linear regression was performed to analyze associations between bone marrow fat levels and sex hormone levels, stratified by gender. Hormone-specific multivariable models, also stratified by gender, controlled for age, visit window, and total percent fat. To assess for interaction, multivariable models for men and women combined were used, controlling for above variables plus gender and an interaction term between hormone level and gender. All analyses were conducted using STATA 14.1 (Stata Corporation, College Station, TX).

3. Results

3.1. Population characteristics

The sample included 244 men and 226 women, who were 74 to 95 years old at BMF measurement. Mean BMF (L1–L4) was 54.1% (SD 8.6%) for men and 54.7% (SD 8.1%) for women. Two women were excluded from estradiol analyses due to high levels of total estradiol. Mean absolute endogenous total hormone levels were 4- and 16-fold higher among men than women, for estradiol and testosterone, respectively (Table 1).

In unadjusted models, BMF was negatively associated with total estradiol in men [−0.28% difference in BMF (%) per 1 pg/ml increase in total estradiol (95% CI: −0.43%, −0.13%)] (Fig. 1A). After adjusting for age, total percent fat, and visit window, BMF remained negatively associated in men [−0.26% (95% CI: −0.41%, −0.11%)] (Table 2). In women, BMF was also negatively associated with total estradiol (Fig. 1B) but the association was not statistically significant in the unadjusted model or the adjusted model [−0.20% (95% CI: −0.55%, 0.15%)]. There was no evidence of interaction between gender and total estradiol (p for interaction = 0.88).

BMF was negatively associated with total testosterone in men in unadjusted [−0.11% difference in BMF (%) per 10 ng/dl increase in total

Download English Version:

https://daneshyari.com/en/article/8625104

Download Persian Version:

https://daneshyari.com/article/8625104

Daneshyari.com