Title

A bone resorption marker as predictor of rate of change in femoral neck size and strength during the menopause transition

Journal

Osteoporosis International, 30(12)

ISSN

0937-941X

Authors

Shieh, A
Ishii, S
Greendale, GA
et al.

Publication Date

2019-12-01

DOI

10.1007/s00198-019-05099-z

Peer reviewed

HHS Public Access

Author manuscript

Osteoporos Int. Author manuscript; available in PMC 2020 December 01.

Published in final edited form as:

Osteoporos Int. 2019 December ; 30(12): 2449–2457. doi:10.1007/s00198-019-05099-z.

A bone resorption marker as predictor of rate of change in femoral neck size and strength during the menopause transition

Albert Shieh, MD[1], **Shinya Ishii, MD**[2], **Gail A. Greendale, MD**[1], **Jane A. Cauley, DrPH**[3], **Carrie Karvonen-Gutierrez**[4], **Arun S. Karlamangla, MD PhD**[1]

[1]Division of Geriatrics, Department of Medicine, David Geffen School of Medicine at University of California, Los Angeles

[2]University of Tokyo; Department of Geriatric Medicine, Graduate School of Medicine

[3]Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh

[4]University of Michigan, Ann Arbor

Abstract

Purpose.—Composite indices of the femoral neck's ability to withstand compressive (compression strength index, CSI) and impact (impact strength index, ISI) forces integrate DXA-derived femoral neck width (FNW), bone mineral density (BMD), and body size. During the menopause transition (MT), FNW increases, and CSI and ISI decrease. This proof-of-concept study assessed whether a bone resorption marker, measured early in the MT, is associated with rates of change in FNW, CSI and ISI during the MT.

Methods.—We used previously collected bone resorption marker (urine collagen type I N-telopeptide [U-NTX]) and femoral neck strength data from 696 participants from the Study of Women's Health Across the Nation (SWAN), a longitudinal study of the MT in a multi-ethnic cohort of community-dwelling women.

Results.—Adjusted for MT stage (pre- vs. early perimenopause), age, body mass index (BMI), bone resorption marker collection time, and study site in multivariable linear regression, bone resorption in pre- and early perimenopause was not associated with transmenopausal decline rate in femoral neck BMD. However, each standard deviation (SD) increase in bone resorption level was associated with 0.2% per year slower increase in FNW (p=0.03), and 0.3% per year faster declines in CSI (p=0.02) and ISI (p=0.01). When restricted to women in early perimenopause, the associations of bone resorption with change in FNW, CSI, and ISI were similar to those in the full sample.

CORRESPONDING AUTHOR/CONTACT FOR REPRINT REQUESTS: Albert Shieh: ashieh@mednet.ucla.edu, 781-254-5034, UCLA Division of Geriatrics, 10945 Le Conte Avenue, Suites 2339-2345, Los Angeles, CA 90095-1687.

CONFLICTS OF INTEREST

AS, SI, GAG, JAC, CKG, and ASK state that they have no conflicts of interest.

Conclusions.—Measuring a bone resorption marker in pre- and early perimenopause may identify women who will experience the greatest loss in bone strength during the MT.

MINI-ABSTRACT

We assessed whether a bone resorption marker, measured early in the menopause transition (MT), is associated with change in femoral neck size and strength during the MT. Higher levels of bone resorption were associated with slower increases in femoral neck size and faster decreases in femoral neck strength.

Keywords

Menopause; biochemical markers of bone turnover; DXA; osteoporosis; general population studies

INTRODUCTION

Osteoporosis is characterized by low bone mass and structural deterioaration of bone tissue, leading to bone fragility, and an increased risk of fractures [1]. To assess an individual's resistance to fracture, clinicians routinely measure bone mineral density (BMD) by dual X-ray absorptiometry (DXA) [1]. BMD is associated with risk of fracture, but does not capture two critical determinants of bone strength. The first is bone size which predicts fracture risk, independent of BMD [2–10]. The second is body weight, as BMD that can withstand the trauma from a fall in an individual with lower body weight may not be adequate in an individual with higher body mass [2,9]. To account for these additional determinants of bone strength, we previously created composite indices of femoral neck strength, which combine BMD with bone size and body size [9]. These indices quantify femoral neck strength relative to the type and amount of trauma that the bone must withstand [9]. These composite strength indices predict fracture independently of BMD, and are correlated with estimates of bone strength by finite element analysis [9–11].

During the menopause transition (MT), loss of BMD is associated with an increase in bone formation at the outer periosteal surface (periosteal apposition), resulting in an increase in bone size [2,12]. However, this increase in bone size is not adequate to maintain bone strength [3,2]. Thus, composite strength indices that reflect the femoral neck's ability to withstand compressive (compression strength index, CSI) and impact (impact strength index, ISI) forces begin to decline rapidly ~1 year before the final menustral period, and continue to decrease in postmenopause with a slight reduction in rate of loss ~2 years after the final menstrual period [2]. We refer to the period of most rapid BMD, CSI and ISI decline, from 1 year before to 2 years after the final menstrual period, as transmenopause [2,13]. Because decline in composite strength indices account for both the extent of BMD loss and the degree to which the associated increase in bone size is able to resist those losses, being able to predict rates of change in femoral neck size, CSI, and ISI may be more important than predicting rate of decline in BMD alone.

The objective of this proof-of-concept study was, therefore, to determine if a bone resorption marker, measured early in the MT, can predict subsequent rate of increase in femoral neck

size (as reflected by femoral neck width [FNW]) and rates of decline in femoral neck CSI and ISI during transmenopause. We used data from the Study of Women's Health Across the Nation (SWAN), a longitudinal study of the MT in a multi-ethnic, community-based cohort of participants with annual measures of the bone resorption marker, urine collagen type I N-telopeptide (U-NTX), BMD, FNW, and femoral neck strength. This study was designed to answer 3 questions: 1) Does bone resorption, assessed by measuring U-NTX in pre- or early perimenopause, predict rate of transmenopausal increase in FNW; 2) Does bone resorption predict rates of transmenopausal decline in composite indices of femoral neck strength during transmenopause; and 3) Does bone resorption predict the rate of loss of femoral neck strength better if measured during early perimenopause (once the MT has begun)?

MATERIALS AND METHODS

Study Sample

SWAN is a multi-center, longitudinal study of the MT in a multi-ethnic cohort of community-based women. At SWAN baseline, participants were between 42 to 52 years of age, in pre- (no change in menstrual regularity in the past year) or early perimenopause (menstruating 3 months prior to screening with decreased regularity in the past year), had an intact uterus with at least 1 ovary, were not pregnant or lactating, and not taking sex steroid hormones. The entire SWAN cohort consisted of 3,302 participants, recruited from seven clinical sites: Boston, MA; Chicago, IL; Detroit, MI; Pittsburgh, PA; Los Angeles, CA; Newark, NJ; and Oakland CA. Chicago and Newark did not perform bone assessments; the SWAN Bone Cohort included 2,413 participants from the remaining five sites. These participants had lumbar spine and femoral neck BMD measured by dual X-ray absorptiometry (DXA) at each visit. The interval between visits was 1 year, except between the 11^{th} and 12^{th}, and the 14^{th} and 15^{th} follow-up visits, which were separated by 2 years. All participants provided written informed consent, and each site obtained institutional review board approval.

The SWAN Hip Strength Sub-Study included 1,986 women who had DXA scans at baseline, and at >2 follow-up visits through the tenth follow-up visit. In these individuals, femoral neck size was measured from archived scans of the hip from the baseline visit, the first visit after each change in clinical MT stage, and the last SWAN visit. There were a total of 6,523 hip scans in these 1,986 women [2]. Among these participants, 921 participants had a known final menstrual period date [9,2]. Then, to calculate the annualized rates of decline during transmenopause, we excluded participants who did not have a follow-up DXA data after the completion of transmenopause (2 years after the final menstrual period, N=122) or reported taking any bone-modifying medications (i.e., sex steroid hormones, medications that affect sex steroid hormone metabolism [GnRH agonists, aromatase inhibitors, selective estrogen receptor modulators], oral glucocorticoids, chemotherapy, and anti-epileptics) at any time prior to the follow-up DXA (N=103). This left us with a study sample of 696 women.

Predictors

Bone resorption was assessed using U-NTX, a bone resorption marker that was commonly measured when SWAN was initiated in 1996, and thus available to us in the SWAN dataset.

Participants provided fasting, non-first voided urine samples before 10AM. Specimens were first stored locally between −20 to −80 degrees Celsius (exact temperature not recorded) for less than one month. Samples were then shipped to the Central Lab (Medical Research Laboratories, Highland Heights, KY), where they were stored at −80 degrees Celsius. U-NTX was quantified using the Osteomark competitive inhibition enzyme immunoassay (nM BCE; Osteomark, Ostex International Inc., Seattle WA; inter-assay CV <12%; intra-assay CV <8%). The Cobas Mira analyzer was used to measure urinary creatinine (mM; Horiba ABX, Montpellier, France; inter-assay CV 4.1%; intra-assay CV 0.6%). U-NTX was normalized to urinary creatinine and expressed in the following units: nM BCE/mM Cr [14–17].

Outcomes

BMD measurement.—Femoral neck BMD was measured by DXA using the Hologic QDR 2000 (Pittsburgh and Oakland) or the Hologic QDR 4500A (Boston, Los Angeles, and Michigan). An anthropomorphic spine phantom was circulated between sites for cross-site calibration. Standard quality control phantom scans were performed prior to each DXA session, and used to adjust for machine drift. Pittsburgh and Oakland upgraded from the Hologic 2000 to 4500A models at the follow-up visit 8. Cross-calibration was achieved at each site by scanning 40 women on their old and new machines at the same visit [13].

Femoral neck size measurements.—Femoral neck axis length (FNAL) and femoral neck width (FNW) were measured from the DXA monitor using pixel sizes provided by Hologic. FNAL is defined as the distance from the lateral margin of the greater trochanter to the apex of the femoral head. FNW is the smallest femoral neck thickness along a line perpendicular to the femoral neck axis [9,2].

Femoral neck strength indices computation.—Composite indices of the femoral neck's ability to withstand compressive (compressive strength index, CSI) and impact (impact strength index, ISI) forces resulting from a fall were derived from DXA-based measures of BMD, bone size (FNAL and FNW), and body size as shown below:

$$\text{Compression strength index (CSI)} = (\text{BMD}*\text{FNW})/\text{body weight}$$

$$\text{Impact strength index (ISI)} = (\text{BMD}*\text{FNW}*\text{FNAL})/(\text{height}*\text{body weight})$$

Both indices are expressed in g/(kg*m). To assess reproducibility, 20 participants were scanned twice on the same day with repositioning. This provided duplicate measures of BMD, FNAL, and FNW. Intraclass correlation coefficients for CSI and ISI were ≥0.98 [2,9].

Rates of decline in femoral neck BMD, size, and strength during transmenopause.—We calculated the annualized rates of change in femoral neck BMD, FNW, and femoral neck strength (CSI and ISI) during transmenopause as the percentage change of each measure from the SWAN baseline visit to the first follow-up visit ~2 years after the final menstrual period, divided by the time (in years) from the start of

transmenopause (T1) to the follow up visit (T2) (Figure 1). Note, that CSI and ISI do not change significantly prior to the start of transmenopause (T1) [2].

Covariates

Body mass index (BMI) was calculated from weight and height [BMI = weight in kilograms/(height in meters)^2]. Clinical MT status was determined by menstrual bleeding patterns. Premenopause was defined as no change in menstrual bleeding pattern. Early perimenopausal was defined as less predictable menstrual cycles, without any gaps of ≥3 months. Other covariates included study site, age (in years), race/ethnicity (self report), and urine collection time (to account for diurnal variation in U-NTX levels) [18].

Statistical Analysis

Descriptive statistics for all variables were generated and distributions of continuous variables were assessed for normality. Differences between pre- vs. early perimenopausal participants at SWAN baseline were assessed by the independent samples t-test (continuous variables) or Chi-square test (categorical variables). Pearson correlations of the rate of transmenopausal decline in femoral neck BMD and rate of increase in FNW with rates of decline in femoral neck composite strength indices, CSI and ISI, were examined.

The first set of regression analyses assessed whether bone resorption at SWAN baseline, when participants were in pre- or early perimenopause, is associated with rate of change in the various components of femoral neck CSI and ISI (Figure 1). We used multivariable linear regression with annualized rates of decline in femoral neck BMD, FNW, CSI or ISI during transmenopause as continuous outcomes in separate models; U-NTX at the SWAN baseline visit as the primary predictor; and MT stage (pre- vs. early perimenopause), age, race/ethnicity, BMI, urine collection time (to account for diurnal variation in U-NTX), and study site as covariates. Covariates were obtained at the time of U-NTX measurement.

Our second set of analyses examined the association between bone resorption assessed specifically in early perimenopause with rates of change in femoral neck strength (Figure 1). We again used multivariable linear regression with annualized transmenopausal rates of change as continuous outcomes; each participant's first available early perimenopausal U-NTX measurement as primary predictor; and age, race/ethnicity, BMI, urine collection time, and study site as covariates. Covariates were obtained at the time of U-NTX measurement. In women who were premenopausal at baseline and transitioned to early perimenopause during study follow-up, the first available early perimenopausal U-NTX measurement occurred within ~1 year of experiencing less predictable menstrual bleeding. In contrast, participants who were already in early perimenopause at SWAN baseline may have been menstruating with decreased regularity for more than 1 year. To determine whether the timing of U-NTX measurement within early perimenopause modifies the association between early perimenopausal U-NTX and decline in femoral neck strength, we additionally tested for an interaction between U-NTX and baseline MT stage.

In supplementary analyses, we examined the associations of U-NTX with the rate of transmenopausal change in cross-sectional femoral neck bone mineral content (BMC, calculated as BMD*FNW, in g/cm). Specifically, we used multivariable linear regression

with rate of transmenopausal change in cross-sectional femoral neck bone mineral content as outcome, U-NTX at SWAN baseline or early perimenopause as primary predictors in separate models, and age, BMI, race/ethnicity, urine collection time, and study site as covariates.

RESULTS

Participant Characteristics at SWAN Baseline

At the SWAN baseline visit, participants had a mean age of 46.9 years (range 42.0 to 52.8 years). Nearly half were white, 26.4% African American, 17.2% Chinese, and 12.2% Japanese. The majority of participants were in premenopause (54.5%; N=381), and the remaining in early perimenopause (N=315). Compared to premenopausal participants, early perimenopausal subjects had slightly higher BMI (27.7 vs. 26.5 kg/m^2, p=0.09), and significantly higher U-NTX levels (36.5 vs. 33.8 nM BCE/mM Cr, p=0.005).

Mean rate of decline in femoral neck BMD during transmenopause was 1.6% per year. FNW increased by a mean rate of 1.1% per year. Mean rates of decline in CSI and ISI were 1.6% per year and 1.7% per year, respectively (Table 1). Of the 174 women whose femoral neck BMD decline rate during transmenopause was in the fastest 25% of the distribution (faster than 3.0% per year), only 79 (45.4%) and 75 (43.1%) were also the fastest 25% of CSI and ISI decliners, respectively. Changes in both BMD and FNW contributed to changes in CSI and ISI. The Pearson correlation coefficients between BMD decline rate and strength index decline rates were 0.35 for CSI (p<0.01) and 0.33 for ISI (p<0.01). The correlation coefficients between rates of change in FNW and in each of the strength indices were 0.42 and 0.39 for CSI (p<0.01) and ISI (p<0.01), respectively. Since on average, FNW increases and strength indices decline, the positive correlations between the two rates of change mean that faster increases in FNW are associated with slower declines in the strength indices.

Baseline Bone Resorption and Rates of Transmenopausal Decline in Femoral Neck Width and Strength

Adjusted for MT stage (pre- vs. early perimenopause), age, BMI, race/ethnicity, urine collection time, and study site in multivariable linear regression, higher U-NTX at SWAN baseline was not significantly associated with subsequent rate of decline in femoral neck BMD during transmenopause (p=0.5), but did predict slower rise (less positive rate of change) in FNW (p=0.03), and faster declines (more negative rates of change) in CSI (p=0.02) and ISI (p=0.01). Specifically, each standard deviation (SD) increment in baseline U-NTX was associated with a 0.2% per year slower rise in FNW, and 0.3% per year faster declines in both CSI and ISI (Table 2).

Participant Characteristics at First Available Early Perimenopausal Visit

All 381 women in the study sample who were premenopausal at baseline had a follow up visit in early perimenopause. The data from their first early perimenopausal visit were combined with the baseline data from the 315 women who were early perimenopausal at baseline, for the second set of analyses. Mean age and BMI were 48.1 years and 27.2 kg/m^2, respectively. Mean U-NTX was 35.6 nM BCE/mM Cr.

First Available Assessment of Bone Resorption in Early Perimenopause and Rates of Transmenopausal Decline in Femoral Neck Width and Strength

In multivariable linear regression, adjusted for age, BMI, race/ethnicity, urine collection time, and study site, the first available U-NTX for participants in early perimenopause was a significant predictor of rates of change in FNW, CSI and ISI. Specifically, each SD increment in early perimenopausal U-NTX was associated with 0.2% per year slower increases in FNW, and 0.4% per year faster declines in both CSI (p=0.01) and ISI (p=0.01) (Table 3). There was no statistically significant interaction between U-NTX and the participants' baseline MT stage (p>0.1 for all), suggesting that the timing of U-NTX measurement within early perimenopause did not modify the association between U-NTX and change in FNW and femoral neck strength.

Supplementary Analyses

Because U-NTX at SWAN baseline and early perimenopause were not significant predictors of change in femoral neck BMD, but were associated with the rate of transmenopausal change in FNW, CSI, and ISI, we additionally examined the association of U-NTX with rate of transmenopausal change in cross-sectional femoral neck BMC (calculated as BMD*FNW, g/cm). In multivariable linear regression adjusted for age, BMI, race/ethnicity, urine collection time, and study site, higher U-NTX was associated with faster declines in cross-sectional femoral neck BMC: Each SD increment in U-NTX at SWAN baseline was associated with a 0.2% per year faster decline in femoral neck cross-sectional BMC (p=0.08); the same increment in U-NTX in early perimenopause was associated with a 0.3% per year faster decline in cross-sectional BMC (p=0.005).

DISCUSSION

Because U-NTX is an early-generation bone resorption marker that is not used in clinical practice, we consider this a proof-of-concept study: it demonstrates the potential value of assessing bone turnover markers in pre- or early perimenopause to forecast MT-related decline in bone strength. We found that although a higher level of resporption in pre- or early perimenopause was not associated with faster decline in femoral neck BMD during transmenopause, it was associated with slower increases in FNW and faster declines in CSI and ISI. The associations were similar whether bone resorption was assessed before or after menstrual bleeding becomes irregular.

While many studies have previously reported that higher bone turnover markers predict faster BMD decline [19–23,14,16,24–27], being able to predict rates of change in FNW, CSI and ISI may be more important because change in these composite strength indices reflects both the extent of BMD loss and the degree to which the concurrent increase in bone size is able to resist those losses [2]. The degree to which bone strength is maintained varies among women, so that fewer than half the women who were fast BMD decliners during transmenopause (i.e., their BMD loss rate was in the fastest quartile) were also fast decliners of CSI and ISI (i.e., in the fastest quartile of CSI and ISI loss) [18]. This is the first study to demonstrate the utitily of early measurement of bone resorption markers (before the occurrence of substantial MT-related bone loss) for predicting MT-related changes in

femoral neck size and bone strength. Further, this is among the first studies to demonstrate the differential utility of a bone resorption marker in predicting changes in the different components of femoral neck strength (size vs. BMD) [28,29].

Our first key finding was that a higher level of bone resorption is associated with slower increases in femoral neck size (assessed by FNW) during transmenopause. One plausible explanation for this finding is that the degree to which femoral neck size increases is determined by not only the amount of bone that is formed through periosteal apposition (which would increase bone size), but also bone that is removed through periosteal resorption (which would decrease bone size) [30–32]. One mechanism by which periosteal bone resorption and formation contribute to changes in bone macroarchitecture is through coordinated modeling drifts [33]. Our findings indirectly suggest that during transmenopause, the relative activity of osteoclastic and osteoblastic drifts are associated with changes in bone size.

Our second key finding was that level of bone resorption is not associated with femoral neck BMD decline rate during transmenopause, but is associated with rates of change in FNW, CSI and ISI over the same period. One possible explanation is that the femoral neck contains substantial amounts of cortical bone, and the periosteal expansion that is associated with endocortical bone loss may not be adequately captured by serial areal BMD measurements by DXA [34]. In contrast, since FNW does increase during the MT, changes in composite strength indices that include FNW, such as CSI and ISI, likely capture cortical bone strength changes better than changes in areal BMD alone. This explanation is supported by our supplementary analyses demonstrating that U-NTX is associated with change in cross-sectional femoral neck bone mineral content. Of note, changes in BMD and FNW were both correlated with changes in the strength indices during transmenopause in our cohort. That both CSI and ISI declined over the MT despite increases in FNW suggests that increases in bone size are not adequate to maintain bone strength in the context of rapid MT-related bone loss. Similar findings have been reported for postmenopausal bone loss [3].

Our third key finding is that the association between level of bone resorption and rates of change in FNW, CSI and ISI during transmenopause were similar, regardless of MT stage (pre- vs. early perimenopause). Of note, we assessed bone resorption at the first available visit in early perimenopause. Participants who were already in early perimenopause at SWAN baseline would have already been in early perimenopause for an indeterminate amount of time. In contrast, participants who were in premenopause at baseline transitioned to early perimenopause during follow-up; in these women, the first early perimenopausal would have occurred ~1 year or less into that MT stage. We found that there was no significant interaction between bone resorption and baseline MT stage in our models, suggesting that the timing of bone resorption assessment within early perimenopause does not significantly modify the association between bone resorption and subsequent change in femoral neck strength. This is important because early perimenopause can last anywhere from several months to many years in different women [35].

Our study has several limitations. The principal one is that only U-NTX was available in the SWAN database. While this bone resorption marker was commonly used at the inception of

SWAN in 1996, serum type I collagen C-telopeptide (S-CTX) is now recommended for clinical research and practice [36]. The major disadvantage of using U-NTX is that urinary measures of bone turnover may be more variable than serum measures because adjusting for urinary creatinine increases variability [14]. However, this shortcoming is conservative, and would lead to non-differential misclassification, and bias our results towards the null. Therefore, the conceptual relevance of our finding, that the degree of bone resorption can predict impending loss of bone strength during the MT, is not diminished. Finally, there are newer technologies for assessing femoral neck strength [37–39]. Nonetheless, CSI and ISI correlate with CT-based estimates of bone strength by finite element analysis [11], and to our knowledge, there are no currently published studies reporting the longitudinal transmenopausal change in femoral neck strength assessed using non-DXA-based technologies.

To conclude, this study confirms that bone resorption (quantified early in the MT, in this instance, using U-NTX) is associated with rates of change in femoral neck size and strength. This finding is important and unique because changes in FNW, CSI, and ISI during transmenopause convey information on the degree to which the increase in bone size is able to maintain bone strength when faced with transmenopausal BMD loss [2]. When assessed during pre- and early perimenopause, higher levels of bone resorption strongly predicted slower increases in FNW and faster declines in CSI and ISI during the most rapid phase of MT-related loss of bone strength. Building on these proof-of-concept findings, future studies will need to confirm these results using S-CTX and finite element analysis, with the ultimate goal of being able to identify women who are at highest risk for rapid loss of femoral neck strength in advance of significant skeletal deterioration.

ACKNOWLEDGEMENTS

The Study of Women's Health Across the Nation (SWAN) has grant support from the National Institutes of Health (NIH), DHHS, through the National Institute on Aging (NIA), the National Institute of Nursing Research (NINR) and the NIH Office of Research on Women's Health (ORWH) (Grants U01NR004061; U01AG012505, U01AG012535, U01AG012531, U01AG012539, U01AG012546, U01AG012553, U01AG012554, U01AG012495). The content of this manuscript is solely the responsibility of the authors and does not necessarily represent the official views of the NIA, NINR, ORWH or the NIH.

Clinical Centers: *University of Michigan, Ann Arbor – Siobán Harlow, PI 2011 – present, MaryFran Sowers, PI 1994–2011*; *Massachusetts General Hospital, Boston, MA – Joel Finkelstein, PI 1999 – present*; *Robert Neer, PI 1994 – 1999; Rush University, Rush University Medical Center, Chicago, IL – Howard Kravitz, PI 2009 – present*; *Lynda Powell, PI 1994 – 2009; University of California, Davis/Kaiser – Ellen Gold, PI*; *University of California, Los Angeles – Gail Greendale, PI*; *Albert Einstein College of Medicine, Bronx, NY – Carol Derby, PI 2011 – present, Rachel Wildman, PI 2010 – 2011; Nanette Santoro, PI 2004 – 2010; University of Medicine and Dentistry – New Jersey Medical School, Newark – Gerson Weiss, PI 1994 – 2004;* and the *University of Pittsburgh, Pittsburgh, PA – Karen Matthews, PI.*

NIH Program Office: *National Institute on Aging, Bethesda, MD – Chhanda Dutta 2016- present; Winifred Rossi 2012–2016; Sherry Sherman 1994 – 2012; Marcia Ory 1994 – 2001; National Institute of Nursing Research, Bethesda, MD – Program Officers.*

Central Laboratory: *University of Michigan, Ann Arbor – Daniel McConnell* (Central Ligand Assay Satellite Services).

Coordinating Center: *University of Pittsburgh, Pittsburgh, PA – Maria Mori Brooks, PI 2012 - present; Kim Sutton-Tyrrell, PI 2001 – 2012; New England Research Institutes, Watertown, MA - Sonja McKinlay, PI 1995 – 2001.*

Steering Committee: Susan Johnson, Current Chair

Chris Gallagher, Former Chair

We thank the study staff at each site and all the women who participated in SWAN.

Additional support for this project provided by NIA through P30-AG028748; UCLA Claude Pepper Older Adults Independence Center (PI: Reuben) funded by the National Institute of Aging (5P30AG028748); NIH/NCATS UCLA CTSI Grant Number UL1TR000124; NIH Grant Number 5RO1AG033067 (PI: Karlamangla and Crandall). Dr. Shieh was supported by the UCLA Specialty Training and Advanced Research Program and the Iris Cantor-UCLA Women's Health Center Executive Advisory Board.

REFERENCES

1. Camacho P, Petak S, Binkley N, Clarke B, Harris S, Hurley D, Kleerekoper M, Lewiecki E, Miller P, Narula H, Pessah-Pollack R, Tangpricha V, Wimalawansa S, Watts N (2016) AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY CLINICAL PRACTICE GUIDELINES FOR THE DIAGNOSIS AND TREATMENT OF POSTMENOPAUSAL OSTEOPOROSIS - 2016--EXECUTIVE SUMMARY. Endocrine Practice 22 (9):1111–1118 [PubMed: 27643923]
2. Ishii S, Cauley JA, Greendale GA, Crandall CJ, Huang MH, Danielson ME, Karlamangla AS (2013) Trajectories of femoral neck strength in relation to the final menstrual period in a multi-ethnic cohort. Osteoporosis International 24 (9):2471–2481 [PubMed: 23436075]
3. Szulc P, Seeman E, Duboeuf F, Sornay-Rendu E, Delmas P (2006) Bone fragility: failure of periosteal apposition to compensate for increased endocortical resorption in postmenopausal women. J Bone Miner Res 21 (12):1856–1863. doi:10.1359/jbmr.060904 [PubMed: 17002580]
4. Riggs B, Melton ILr, Robb R, Camp J, Atkinson E, Peterson J, Rouleau P, McCollough C, Bouxsein M, Khosla S (2004) Population-based study of age and sex differences in bone volumetric density, size, geometry, and structure at different skeletal sites. J Bone Miner Res 19 (12):1945–1954. doi: 10.1359/JBMR.040916 [PubMed: 15537436]
5. Balena R, Shih M, Parfitt A (1992) Bone resorption and formation on the periosteal envelope of the ilium: a histomorphometric study in healthy women. J Bone Miner Res 7 (12):1475–1482. doi: 10.1002/jbmr.5650071216 [PubMed: 1481733]
6. Seeman E (2003) Periosteal bone formation--a neglected determinant of bone strength. The New England Journal of Medicine 349 (4):320–323 [PubMed: 12878736]
7. Ahlborg H, Johnell O, Turner C, Rannevik G, Karlsson M (2003) Bone loss and bone size after menopause. N Engl J Med 349 (4):327–334. doi:10.1056/NEJMoa022464 [PubMed: 12878739]
8. Leslie W, Lix L, Majumdar S, Morin S, Johansson H, Odén A, McCloskey E, Kanis J (2017) Total Hip Bone Area Affects Fracture Prediction With FRAX® in Canadian White Women. J Clin Endocrinol Metab 102 (11):4242–4249. doi:10.1210/jc.2017-01327 [PubMed: 29092086]
9. Karlamangla AS, Barrett-Connor E, Young J, Greendale GA (2004) Hip fracture risk assessment using composite indices of femoral neck strength: the Rancho Bernardo study. Osteoporosis International 15 (1):62–70 [PubMed: 14605798]
10. Ishii S, Greendale GA, Cauley JA, Crandall CJ, Huang M-H, Danielson ME, Karlamangla AS (2012) Fracture risk assessment without race/ethnicity information. The Journal of Clinical Endocrinology & Metabolism 97 (10):3593–3602 [PubMed: 22865903]
11. Danielson M, Beck T, Karlamangla A, Greendale G, Atkinson E, Lian Y, Khaled A, Keaveny T, Kopperdahl D, Ruppert K, Greenspan S, Vuga M, Cauley J (2013) A comparison of DXA and CT based methods for estimating the strength of the femoral neck in post-menopausal women. Osteoporos Int 24 (4):1379–1388. doi:10.1007/s00198-012-2066-y [PubMed: 22810918]
12. Ahlborg HG, Johnell O, Turner CH, Rannevik G, Karlsson MK (2003) Bone loss and bone size after menopause. New England Journal of Medicine 349 (4):327–334 [PubMed: 12878739]
13. Greendale G, Sowers M, Han W, Huang M, Finkelstein J, Crandall C, Lee J, Karlamangla A (2012) Bone mineral density loss in relation to the final menstrual period in a multiethnic cohort: Results from the Study of Women's Health Across the Nation (SWAN). J Bone Miner Res 27 (1): 111–118. doi:10.1002/jbmr.534 [PubMed: 21976317]

14. Shieh A, Ishii S, Greendale G, Cauley J, Lo J, Karlamangla A (2016) Urinary N-Telopeptide and Rate of Bone Loss Over the Menopause Transition and Early Postmenopause. J Bone Miner Res. doi:10.1002/jbmr.2889
15. Sowers M, Zheng H, Greendale G, Neer R, Cauley J, Ellis J, Johnson S, Finkelstein J (2013) Changes in bone resorption across the menopause transition: effects of reproductive hormones, body size, and ethnicity. J Clin Endocrinol Metab 98 (7):2854–2863. doi:10.1210/jc.2012-4113 [PubMed: 23666961]
16. Cauley JA, Danielson ME, Greendale GA, Finkelstein JS, Chang Y-F, Lo JC, Crandall CJ, Neer RM, Ruppert K, Meyn L, Prairie BA, Sowers MR (2012) Bone resorption and fracture across the menopausal transition: the Study of Women's Health Across the Nation. Menopause 19 (11):1200 [PubMed: 22850443]
17. Shieh A, Han W, Ishii S, Greendale G, Crandall C, Karlamangla A (2016) Quantifying the Balance Between Total Bone Formation and Total Bone Resorption: An Index of Net Bone Formation. J Clin Endocrinol Metab 101 (7):2802–2809. doi:10.1210/jc.2015-4262 [PubMed: 27336357]
18. Vasikaran SCC, Eastell R, Griesmacher A, Morris HA, Trenti T, Kanis JA. (2011) International Osteoporosis Foundation and International Federation of Clinical Chemistry and Laboratory Medicine position on bone marker standards in osteoporosis. Clinical Chemistry and Laboratory Medicine 49 (8):1271–1274 [PubMed: 21605012]
19. Dresner-Pollak R, Parker R, Poku M, Thompson J, Seibel M, Greenspan S (1996) Biochemical markers of bone turnover reflect femoral bone loss in elderly women. Calcified Tissue International 59 (5):328–333 [PubMed: 8849397]
20. Garnero P, Sornay-Rendu E, Chapuy M, Delmas P (1996) Increased bone turnover in late postmenopausal women is a major determinant of osteoporosis. Journal of Bone and Mineral Research 11 (3):337–349 [PubMed: 8852944]
21. Garnero P, Hausherr E, Chapuy M, Marcelli C, Grandjean H, Muller C, Cormier C, Breart G, Meunier P, Delmas P (1996) Markers of bone resorption predict hip fracture in elderly women: the EPIDOS Prospective Study. Journal of Bone and Mineral Research 11 (10):1531–1538 [PubMed: 8889854]
22. Ebeling P, Atley L, Guthrie J, Burger H, Dennerstein L, Hopper J, Wark J (1996) Bone turnover markers and bone density across the menopausal transition. J Clin Endocrinol Metab 81 (9):3366–3371. doi:10.1210/jcem.81.9.8784098 [PubMed: 8784098]
23. Rogers A, Hannon R, Eastell R (2000) Biochemical markers as predictors of rates of bone loss after menopause. Journal of Bone and Mineral Research 15 (7):1398–1404 [PubMed: 10893690]
24. Štěpán J, Pospichal J, Presl J, Pacovský V (1987) Bone loss and biochemical indices of bone remodeling in surgically induced postmenopausal women. Bone 8 (5):279–284 [PubMed: 3501301]
25. Garnero P, Sornay-Rendu E, Duboeuf F, Delmas P (1999) Markers of bone turnover predict postmenopausal forearm bone loss over 4 years: the OFELY study. Journal of Bone and Mineral Research 14 (9):1614–1621 [PubMed: 10469291]
26. Löfman O, Magnusson P, Toss G, Larsson L (2005) Common biochemical markers of bone turnover predict future bone loss: a 5-year follow-up study. Clinica Chimica Acta 356 (1):67–75
27. Bauer D, Sklarin P, Stone K, Black D, Nevitt M, Ensrud K, Cummings S (1999) Biochemical markers of bone turnover and prediction of hip bone loss in older women: the study of osteoporotic fractures. Journal of Bone and Mineral Research 14 (8):1404–1410 [PubMed: 10457273]
28. Marques E, Gudnason V, Lang T, Sigurdsson G, Sigurdsson S, Aspelund T, Siggeirsdottir K, Launer L, Eiriksdottir G, Harris T (2016) Association of bone turnover markers with volumetric bone loss, periosteal apposition, and fracture risk in older men and women: the AGES-Reykjavik longitudinal study. Osteoporos Int 27 (12):3485–3494. doi:10.1007/s00198-016-3675-7 [PubMed: 27341810]
29. Marques E, Gudnason V, Sigurdsson G, Lang T, Johannesdottir F, Siggeirsdottir K, Launer L, Eiriksdottir G, Harris T (2016) Are bone turnover markers associated with volumetric bone density, size, and strength in older men and women? The AGES-Reykjavik study. Osteoporos Int 27 (5):1765–1776. doi:10.1007/s00198-015-3442-1 [PubMed: 26630978]

30. Orwoll ES (2003) Toward an expanded understanding of the role of the periosteum in skeletal health. J Bone Miner Res 18 (6):949–954. doi:10.1359/jbmr.2003.18.6.949 [PubMed: 12817746]
31. Epker BN, Frost HM (1965) A histological study of remodeling at the periosteal, haversian canal, cortical endosteal, and trabecular endosteal surfaces in human rib. The Anatomical record 152 (2): 129–135 [PubMed: 5842156]
32. Orwoll E, Orwoll S, Kohama S, Evans G, Turner R (2002) Periosteal bone formation and resorption are both active at the femoral neck: Mechanisms for change in bone size. J Bone Miner Res 17 (S1):S300
33. Frost HM (1982) Mechanical determinants of bone modeling. Metab Bone Dis Relat Res 4 (4): 217–229 [PubMed: 6763662]
34. Nickolas T, Leonard M, Shane E (2008) Chronic kidney disease and bone fracture: a growing concern. Kidney Int 74 (6):721–731. doi:10.1038/ki.2008.264 [PubMed: 18563052]
35. Greendale G, Ishii S, Huang M, Karlamangla A (2013) Predicting the timeline to the final menstrual period: the study of women's health across the nation. J Clin Endocrinol Metab 98 (4): 1483–1491. doi:10.1210/jc.2012-3732 [PubMed: 23533245]
36. Vasikaran S, Eastell R, Bruyère O, Foldes A, Garnero P, Griesmacher A, McClung M, Morris H, Silverman S, Trenti T, Wahl D, Cooper C, Kanis J (2011) Markers of bone turnover for the prediction of fracture risk and monitoring of osteoporosis treatment: a need for international reference standards. Osteoporos Int 22 (2):391–420. doi:10.1007/s00198-010-1501-1 [PubMed: 21184054]
37. Engelke K, Lang T, Khosla S, Qin L, Zysset P, Leslie WD, Shepherd JA, Shousboe JT (2015) Clinical Use of Quantitative Computed Tomography-Based Advanced Techniques in the Management of Osteoporosis in Adults: the 2015 ISCD Official Positions-Part III. J Clin Densitom 18 (3):393–407. doi:10.1016/j.jocd.2015.06.010 [PubMed: 26277853]
38. Nishiyama KK, Shane E (2013) Clinical imaging of bone microarchitecture with HR-pQCT. Curr Osteoporos Rep 11 (2):147–155. doi:10.1007/s11914-013-0142-7 [PubMed: 23504496]
39. Zysset PK, Dall'ara E, Varga P, Pahr DH (2013) Finite element analysis for prediction of bone strength. BoneKEy reports 2:386. doi:10.1038/bonekey.2013.120 [PubMed: 24422106]

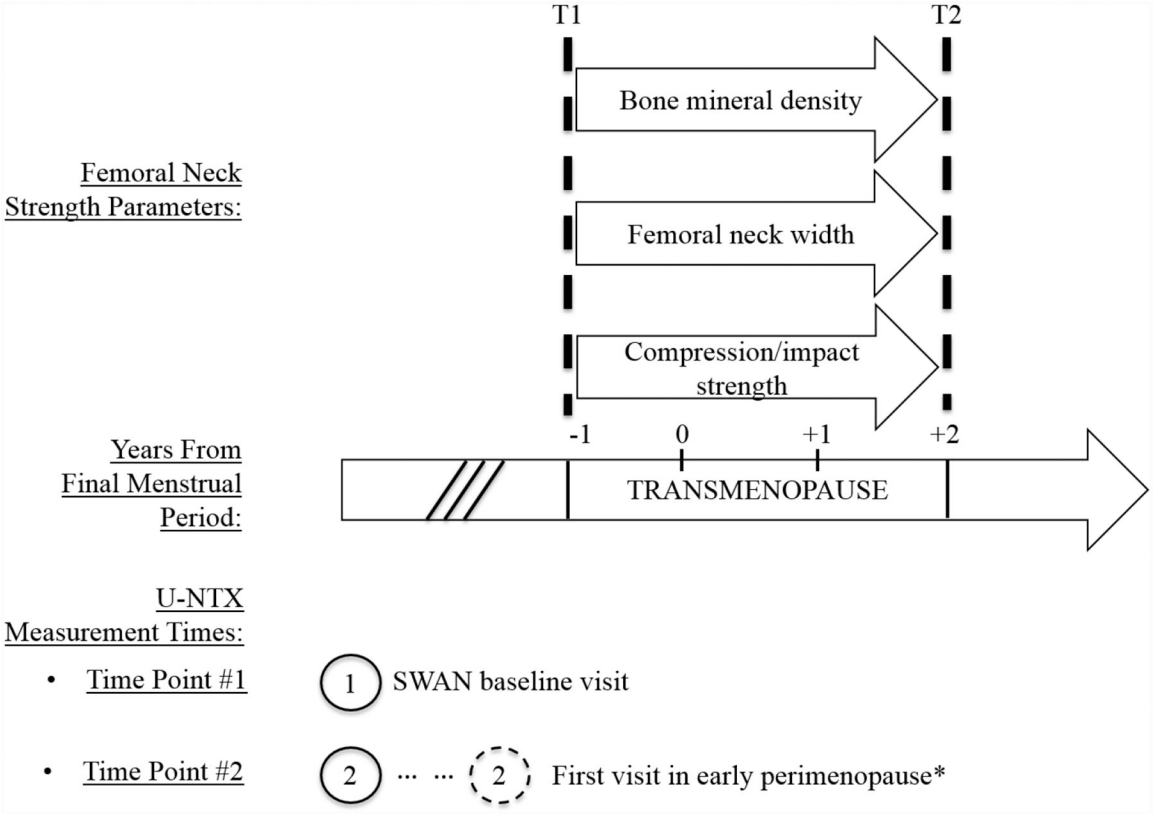

Figure 1. The time period over which rates of change in femoral neck strength parameters were assessed.

T1 refers to 1 year before the final menstrual period when rapid bone loss begins. T2 refers to 2 years after the final menstrual period when rate of bone loss slows slightly. The period between T1 and T2 has been termed transmenopause. **The two time points at which U-NTX was assessed.** 1) We tested the associations between U-NTX measured at SWAN baseline when women are pre- or early perimenopausal (<3 months between less predictable cycles) with rates of change in femoral neck bone mineral bone density, width, compression strength index, and impact strength index during transmenopause. 2) We also tested the ability of the first available U-NTX from early perimenopause to predict compression and impact strength recognizing that in clinical practice, clinicians may be reluctant to check U-NTX until there are clear indications of the menopause transition (e.g., less predictable menstrual cycles). *For participants who were already in early perimenopause at SWAN baseline, the first available early perimenopausal U-NTX was from the baseline visit. For women who were in premenopause at baseline and transitioned to early perimenopause during the study, the first available early perimenopausal U-NTX was from a follow-up visit. Note that early perimenopausal women could have been anywhere between several years to several months before the final menstrual period.

Table 1.

Descriptive statistics[a] for analytic sample at study baseline[b]; Study of Women's Health Across the Nation (SWAN)

	Study Sample N=696
Age (years)	46.9 (2.6)
Race/Ethnicity	
African American	184 (26.4)
White	307 (44.1)
Chinese	120 (17.2)
Japanese	85 (12.2)
Body mass index (kg/m^2)	27.0 (6.8)
N-telopeptide, urine (nM BCE/mM Cr)	35.1 (17.0)
Annualized percent change in femoral neck strength parameters during transmenopause	
Femoral neck bone mineral density (%/year)	−1.6 (2.1)
Femoral neck width (%/year)	+1.1 (1.8)
Femoral neck compression strength index (%/year)	−1.6 (3.7)
Femoral neck impact strength index (%/year).	−1.7 (3.8)

[a]Count (percentage) for categorical variables; mean (standard deviation) for continuous variables. All variables (other than rate of change) were measured at SWAN baseline visit.

[b]N=696. All participants were pre- or early perimenopausal at SWAN baseline.

Table 2.

Adjusted associations[a] of urinary N-telopeptide measured at SWAN baseline with rates of change in femoral neck strength parameters during transmenopause[b]

	β-coefficient (95% Confidence Interval)	**p-value**
Femoral neck bone mineral density (g/cm^2)	−0.05 (−0.22, 0.11)	0.5
Femoral neck width (m)	−0.15 (−0.29, −0.01)	0.03
Femoral neck compression strength index (g/[kg*m])	−0.34 (−0.62, −0.05)	0.02
Femoral neck impact strength index (g/[kg*m])	−0.34 (−0.66, −0.06)	0.01

[a]Increment in annualized percent change in femoral neck strength parameter per standard deviation increment in SWAN baseline urinary N-telopeptide (17.0 nM BCE/mM Cr) adjusted for menopause transition stage (pre- vs. early perimenopause), age, ethnicity, body mass index, sample collection time, and study site.

[b]Femoral neck strength parameters include femoral neck bone mineral density (g/cm^2), femoral neck width (m), femoral neck compression strength index (g/[kg*m]) and impact strength index (g/[kg*m]).

Table 3.

Adjusted associations[a] of urinary N-telopeptide measured during early perimenopause[b] with rates of change in femoral neck strength parameters during transmenopause[c]

	β-coefficient (95% Confidence Interval)	**p-value**
Femoral neck bone mineral density (g/cm^2)	−0.16 (−0.33, 0.02)	0.1
Femoral neck width (m)	−0.16 (−0.30, −0.02)	0.02
Femoral neck compression strength index (g/[kg*m])	−0.40 (−0.70, −0.11)	0.01
Femoral neck impact strength index (g/[kg*m])	−0.45 (−0.75, −0.14)	0.01

[a]Increment in annualized percent change in femoral neck strength parameter per standard deviation increment in early perimenopausal urinary N-telopeptide (17.7 nM BCE/mM Cr) adjusted for age, ethnicity, body mass index, sample collection time, and study site.

[b]The first available urinary N-telopeptide from early perimenopause was used. For participants who were already in early perimenopause at SWAN baseline, the first available early perimenopausal U-NTX was from the baseline visit. For women who were in premenopause at baseline and transitioned to early perimenopause during the study, the first available early perimenopausal U-NTX was from a follow-up visit. The mean (SD) number of years from the time of this U-NTX measurement to the start of transmenopause was 3.4 (3.1).

[c]Femoral neck strength parameters include femoral neck bone mineral density (g/cm^2), femoral neck width (m), femoral neck compression strength index (g/[kg*m]) and impact strength index (g/[kg*m]).