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Calcium Plus Vitamin D Supplementation Has Limited Effects on Femur Geometric Strength in Older Postmenopausal Women: The Women's Health Initiative

Rebecca D Jackson, MD¹, Nicole C. Wright, MPH², Thomas J. Beck, ScD³, Duane Sherrill, PhD², Jane A. Cauley, DrPH MPH⁴, Cora E. Lewis, MD⁵, Andrea Z. LaCroix, PhD MPH⁶, Meryl S. LeBoff, MD⁷, Scott Going, PhD⁸, Tamsen Bassford, MD⁹, and Zhao Chen, PhD, MPH²

¹College of Medicine, Division of Endocrinology, Diabetes and Metabolism and Center for Clinical and Translational Science, The Ohio State University, Columbus OH

²Mel and Enid Zuckerman College of Public Health, University of Arizona, Tucson, AZ

³Department of Radiology, The Johns Hopkins University, Baltimore, MD

⁴Department of Epidemiology, University of Pittsburgh, Pittsburgh, PA

⁵Division of Preventive Medicine, University of Alabama at Birmingham, Birmingham AL

⁶Fred Hutchinson Cancer Research Center, Seattle, WA

⁷Brigham and Women's Hospital, Endocrine, Diabetes, and Hypertension Division, Harvard Medical School, Brigham and Women's Hospital, Boston, MA

⁸Department of Nutritional Sciences, College of Agriculture and Life Sciences, University of Arizona, Tucson, AZ

⁹Department of Family and Community Medicine, College of Medicine, University of Arizona, Tucson, AZ

Abstract

Purpose—Calcium plus vitamin D (CaD) supplementation has a modest but significant effect on slowing loss of femoral bone mass and reducing risk of hip fractures in adherent postmenopausal women. The goal of this study was to determine if CaD supplementation influences hip structural parameters that are associated with fracture risk.

Methods—We studied 1,970 postmenopausal women enrolled in the Women's Health Initiative randomized controlled trial of CaD at one of three bone mineral density (BMD) clinical centers. Hip structural analysis software measured BMD and strength parameters on DXA scans at three

Corresponding Author: Rebecca D Jackson MD, The Ohio State University, 485 McCampbell Hall, 1581 Dodd Drive, Columbus, OH 43210, Phone: 614-292-3800, Fax number: 614-292-8289, jackson.20@osu.edu.

Conflict of Interests

The Hip Structure Analysis software method has been licensed to Hologic Inc. by the Johns Hopkins University (Dr. Beck's Institution). Dr. Beck has also founded a company to build DXA systems specialized to measure bone geometry. Dr. Cauley has received research grants from Novartis and Pfizer regarding fracture outcome trials, and also received consultant fees from Novartis for role on the HORIZON Steering Committee. Dr. LaCroix serves on the Scientific Advisory Board for the PEARL Trial, a multi-center international trial of lasofofenone sponsored by Pfizer, Inc, and also serves as a consultant and site Principal Investigator to design and implement the Global Longitudinal study of Osteoporosis in Women (GLOW), which is funded by the Alliance for Better Bone Health (Proctor and Gamble and sanofi-aventis). All other investigators have no financial conflicts of interests.

regions: femoral narrow neck, intertrochanteric and shaft. Random effects models were used to test the average differences in hip BMD and geometry between intervention and placebo.

Results—There was greater preservation of hip BMD at the narrow neck with CaD relative to placebo across six years of intervention. CaD also altered the underlying cross-sectional geometry at the narrow neck in the direction of greater strength with small increases in cross-sectional area and section modulus, and a decrease in buckling ratio with CaD relative to placebo. While trends at both the intertrochanter and shaft regions were similar to those noted at the narrow neck, no significant intervention effects were evident. There was no significant interaction of CaD and age or baseline calcium levels for hip structural properties.

Conclusions—CaD supplementation is associated with modest beneficial effects on hip structural features at the narrow neck, which may explain some of the benefit of CaD in reducing hip fracture risk.

Keywords

Calcium and Vitamin D Supplementation; Bone Strength; Postmenopausal Women; Hip Structure

INTRODUCTION

Osteoporosis is a major public health problem [1]. Fractures are the primary clinical consequence of osteoporosis, and four out of ten women will suffer a fracture after the age of fifty [2]. Hip fractures are the most serious outcome of osteoporosis and are one of the most disabling consequences of aging in women [3, 4]. Of those women who suffer a hip fracture, 10–45% will die within the year following their fracture [5]. In order to reduce the burden of this disease, efforts have focused on identifying interventions that might reduce the population-based risk for this common disease.

Calcium and vitamin D is one nutritional factor being studied in fracture intervention studies, as many segments of the American population, including older women, are consuming inadequate dietary amounts of calcium and vitamin D. The results of studies exploring the effects of calcium plus vitamin D supplementation on reduction of hip and total fractures have been mixed [6]. The Women's Health Initiative (WHI) randomized, controlled clinical trial of calcium plus vitamin D supplementation (CaD) demonstrated a non-statistically significant 12% reduction in hip fractures with no effect of CaD on wrist, clinical vertebral or total fractures. In sub-group analyses however, a significant 21% decrease in hip fractures was noted for women over age 60 and a 29% reduction in adherent women [7]. Several recent meta-analyses are consistent with the above findings and suggest modest benefits of CaD on bone mineral density (BMD) and fractures, particularly with calcium intakes over 1200 mg and with vitamin D supplementation greater than 800 units daily [6].

CaD may act through several pathways to reduce the risk for hip fracture, including, reducing the risk for falling [8–15]; having positive effects on calcium balance [12, 16]; reducing bone resorption through modifying parathyroid hormone secretion [12, 17, 18], and preserving bone mineral density (BMD) [7, 12, 19]. However, BMD is a limited surrogate marker for improvements in bone strength as it does not express the measured mineral in non-ambiguous format that can be interpreted mechanically [20].

Recent studies have suggested that therapeutic interventions that reduce fracture risk, such as estrogen, raloxifene or bisphosphonates, may improve the structural geometry properties of the proximal femur [21–25]. These structural properties can be estimated from analyses of hip scans using dual-energy X-ray absorptiometry (DXA) [26, 27], and differences in

structural properties have been found between fracture cases and controls [28, 29]. Recently, a study among the participants in the Women's Health Initiative (WHI) has demonstrated an independent contribution of hip structure parameters from bone density to the risk of hip fracture [30], providing evidence of the importance of having both material and structural measures in examining fracture risk and mechanisms for fracture risk reduction.

The purpose of the current study is to use data from the BMD sub-cohort of women enrolled in the WHI randomized, controlled clinical trial of calcium plus vitamin D supplementation to examine the hypothesis that CaD supplementation has a beneficial effect on hip structural geometry. We further hypothesize that the effects of CaD on hip structure will be greater in older women consistent with the greater effect of CaD on hip fracture among women over 60 in the WHI.

METHODS

The Women's Health Initiative Study

The WHI was a large study designed to address major causes of death and disability in older postmenopausal women. It included a combination of four nested clinical trials and an observational study designed to investigate whether hormone therapy (estrogen-alone or estrogen plus progestin), low fat diet, and/or calcium plus vitamin D supplements reduced the risk of major diseases in older women including heart attack and stroke, breast and colorectal cancer and osteoporotic fracture. Postmenopausal women age 50–79 years old who were not likely to change residence and had no evidence of a medical condition associated with predicted survival of less than 3 years at the time of enrollment were recruited from 40 clinical centers nationwide between 1993 and 1998. All participants provided written consent to participate in the WHI. Details regarding the inclusion and exclusion criteria, recruitment procedures, participant characteristics, randomization, blinding, and follow-up have been previously published [31, 32]. The University of Arizona's Institutional Review Board approved this project.

WHI CaD trial

The WHI CaD trial was a randomized double-blind, placebo-controlled clinical trial of calcium (1000 mg elemental calcium in the form of calcium carbonate) with 400 units of vitamin D₃ (cholecalciferol) in divided daily doses versus placebo. Participants who were enrolled in the WHI low-fat Dietary Modification trial, one of the WHI Hormone Therapy trials or in both were recruited into the CaD trial at their 1st or 2nd annual follow up visit (n=36,281). The primary outcome of the CaD trial was hip fracture; total fractures and colorectal cancer were pre-specified secondary outcomes. The trial was designed to last for an average of 7.0 years of follow up.

Questionnaires were used at baseline and follow-up to collect information on demographics, lifestyle and health behavioral factors and clinical risk factors for osteoporotic fracture. Total daily calcium intake was defined as the sum of the dietary calcium intake assessed by the use of a modification of the Block food frequency questionnaire [33], the intake of calcium plus vitamin D supplements in the previous two weeks and the intake of calcium from prescription medication. Total vitamin D intake was similarly assessed.

A sub-group of 2,350 women (1,179 in the CaD group and 1,171 in the placebo group) at 3 of the 40 clinical centers (Pittsburgh, PA; Birmingham, AL; and Tucson/Phoenix, AZ) chosen to maximize racial diversity underwent DXA scans (QDR 2000, 2000+ or 4500W, Hologic; Waltham MA) of the spine (L2,3 and 4), hip and total body. This DXA sub-group became the cohort used for the analysis of hip structural geometry.

BMD was measured at the CaD randomization visit, and at annual visits 3 and 6 according to standard protocols [32]. Three Hologic phantoms were exchanged among the DXA centers and measured in array mode five times, one each day for five consecutive days to assess cross-calibration. Spine hip and linearity phantoms were in close agreement as previously described. For hip structural geometry measurements, a separate cross-calibration was conducted using a special phantom provided by Dr. Beck from Johns Hopkins University.

Hip Structural Analysis

Hip structural analysis (HSA) was conducted on archived scans at the Johns Hopkins University as previously described [26, 27]. The HSA program computes geometry from 5 parallel lines, 1 pixel (~1mm) apart, traversing the bone axis at each of three femur cross-sections; the Narrow Neck across the femur neck at its narrowest point; the Shaft, across the shaft at a distance of 1.5 times minimum neck width distal to the intersection of the neck and shaft axes; and the Intertrochanteric along the bisector of the angle produced by neck and shaft axes.

HSA is based upon the concept that a line of pixel values in a bone mass image is a projection of the mineral in the corresponding cross-section [34]. Assuming that the mineral is distributed as it is in adult cortical bone, the profile integral is a measure of the total bone surface, thus its resistance to axially directed loads. The distribution of the mineral along the profile, after correcting for mineralization, is used to derive the cross-sectional moment of inertia (CSMI) for resisting bending in the image plane. The CSMI can be used to evaluate bending stress at any point within the cross-section. The maximum bending stress, defined at the surface farthest from the center of mass ($d_{\max}$), is inversely related to the section modulus, computed as $\text{CSMI}/d_{\max}$. An estimate of buckling ratio is generated as an index of susceptibility to local cortical buckling under loads that produce compression. Wall thickness for a buckling ratio can only be crudely estimated from DXA data using assumptions of shape and proportion of measured bone in the cortex but this parameter has been shown to provide a mechanical explanation for the predictive value of low BMD in elderly bones [28, 29]. The HSA program also computes conventional BMD, bone outer diameter, as well as other parameters not used in the present study

Statistical analysis

Descriptive analyses and group comparisons (t-test for continuous variables or chi-squared test for categorical variables) were conducted by intervention group for selected characteristics of the study participants at baseline. The intention-to-treat principle was used in the analyses to test CaD intervention effects on BMD and hip structural geometry measurements. The mean BMD and hip geometry measurements were compared cross-sectionally by treatment group at each time point (baseline, year 3, and year 6). Intervention effects of CaD were first examined by testing the differences in percent of changes from baseline to year 6 for BMD and the hip structural geometry measurements between the placebo group and the CaD intervention group using linear regression models. Then random effects models (REM), a type of linear mixed effects model which uses all observations at different time points in a cohort study, were used to test the average differences in hip BMD and geometry between intervention and placebo groups. In addition any temporal differences (differences in the slope over time) between the two groups were also examined using REM. In evaluating potential confounding factors and interaction terms, models examined baseline age (continuous and dichotomized at age>60), height, ethnicity, whole body BMC, whole body bone area, percent lean mass, physical activity, baseline hormone use, and HT trial randomization. Marginal analyses were used to evaluate each covariate separately, then variables with $p<0.2$ were examined in the models with other covariates.

Backward selection techniques were used to remove covariates and finalize the model. Sub-group analyses examining the interaction of the intervention with age, baseline calcium intake, and trial adherence were performed. Predicted values normalized to baseline were used to graphically portray the results of the final REM models. STATA v.10 (College Station, TX) was used for all the data analysis.

RESULTS

Baseline Characteristics

Out of 2,350 women in the CaD trial who were in the DXA cohort, a total of 1,970 women (991 in the CaD group and 979 in the placebo group) completed at least 2 hip DXA scans and were included in the hip geometry analyses. Demographic characteristics, health behaviors and medical history were well balanced between groups (Table 1). These women had a mean (SD) age of 62.0 (7.1) and a mean body mass index of 28.8 (5.5) kg/m². The average total daily calcium intake was approximately 1,044.1 mg and a third were currently using hormone therapy [320 (32.7%) in CaD placebo and 304 (30.7%) in CaD intervention group]. Baseline total body, hip and spine BMD were modestly but significantly higher in the CaD intervention versus placebo group. Three femur geometric properties, the cross-sectional area, section modulus and buckling ratio also differed between CaD and placebo at baseline (Table 2).

Changes in BMD and Hip Geometry due to Intervention

There was greater preservation of hip BMD at the femoral narrow neck with CaD relative to placebo across five years of intervention; no significant effect of CaD was noted at either the intertrochanter or femoral shaft (Figure 1). The BMD effect at the narrow neck was seen as early as annual visit 3, two years after CaD randomization, and persisted through annual visit 6 (Figure 2).

CaD also altered the underlying femur cross-sectional geometry at the narrow neck in the direction of greater strength. When comparing the percent difference between baseline and year 6, cross-sectional area significantly increased relative to placebo ($p < 0.05$) at the narrow neck (Figure 1). No benefit was evident for the outer diameter, buckling ratio or section modulus. In contrast to the narrow neck region, there were no significant effects of CaD at the intertrochanter or femoral shaft regions for any of the geometric properties measured.

Longitudinal Analysis On Intervention Effects

The effects of CaD supplementation over time based on the REM are shown in Table 3. From the baseline CaD enrollment visit to annual visit 3 (2 year interval), small increases in BMD, cross-sectional area, and section modulus, and a decrease in buckling ratio at the narrow neck were seen with CaD relative to placebo in the crude and adjusted models. The results did not change when the model was fully adjusted for age, ethnicity, HT use, percent lean body mass, and WHI-CT assignment in addition to the baseline value, height, and weight (data not shown). By annual visit 6, there was a subsequent loss of some of the gains between baseline and annual visit 3 for all geometric properties, with the exception of outer diameter with no evidence of significant differences in the rates of gain (or loss) over time between the placebo and CaD intervention groups (Figure 2). Even with minor loss of the benefit gained, based on the random effects model CaD intervention provided a small, yet statistically significant, improvement in bone strength. While trends at both the intertrochanter and femoral shaft regions were similar to those noted at the narrow neck, no significant longitudinal effects of CaD intervention on BMD and hip geometry at these two other regions were evident (data not shown).

Sub-group analyses of intervention effects

Although the effect of CaD on hip fracture varied with age reaching a significant 21% decrease in risk for women > 60 years of age in the WHI CaD trial, there was no significant interaction of CaD and age for hip structural properties (data not shown). There was also no difference in the effects of CaD based on reported baseline dietary and supplemental calcium intake levels.

Participants with 80% or greater compliance with study protocol were considered adherent. A total of 968 women (CaD placebo=500; CaD intervention=468) were adherent throughout the entire 5 years of examination. Slightly stronger CaD effects were seen in this population, especially in the intertrochanter and shaft regions although the overall results of the adherence analyses were similar to the entire cohort (data not shown).

DISCUSSION

CaD has been shown to reduce the risk of hip fracture in older postmenopausal women [6]. In this prospective randomized controlled trial of CaD supplementation, the previously demonstrated improvement in hip BMD relative to placebo was seen at the narrow neck with a non-significant trend towards improvement in BMD at the intertrochanter and femoral shaft regions of the proximal femur.

The ability of the hip to withstand the force of fracture should be directly evident in cross-sectional geometry. Applying HSA to DXA to explore the mechanical implications of CaD in this study revealed limited effects of CaD on measurements of femur geometric properties in crude and adjusted models. Over the follow-up period, BMD and geometric properties of cross-sectional area and section modulus increased significantly at the narrow neck consistent with greater strength. Similarly, with CaD intervention, buckling ratio significantly decreased over the 6 years.

Overall, there were no detectable benefits of CaD on geometric properties at either the intertrochanteric or femoral shaft regions. The lack of statistically significant effect at these other hip regions differs from the improved effects noted at all three HSA regions with hormone therapy and alendronate [21, 22]. It should be noted that the magnitude of the treatment effect was greater in the latter studies. These results however are consistent with the reported lack of effect of CaD on reducing risk of fracture at other skeletal sites [7], and thus the lack of effect at the intertrochanteric and shaft regions could also reflect the difference in fracture risk reduction with CaD relative to the greater reduction of both vertebral and non-vertebral fractures reported with estrogen [35, 36] and alendronate [37, 38].

Previous studies have postulated that the generalized expansion of femur diameter with aging helps to preserve bending resistance (section modulus) in the presence of net bone loss until this compensatory change can no longer overcome the concurrent effect of endosteal resorption, eventually resulting in cortical thinning and mechanical instability [39]. In a previously paper using data within the same WHI sub-cohort, a significant independent contribution of femur diameter at the intertrochanteric region to hip fracture risk was observed [30]. In this study, we demonstrate a modest but non-significant attenuation of outer diameter expansion with CaD and a small significant reduction in buckling ratio. Lack of an apparent effect on buckling ratio at the intertrochanteric region, reduces enthusiasm in the conclusion that CaD lowers susceptibility to local buckling.

This is the first longitudinal study to examine HSA parameters derived from DXA in relation to CaD supplementation in older adults. In this study, the effects of CaD on

geometric properties at the narrow neck correspond with an increase in bone strength at an important fracture site. Conceivably tissue material strength may be improved by CaD treatment in ways that would not be evident in DXA measurements of geometry. Indeed, Boivin noted some increase in average tissue mineralization in iliac biopsies of women on estrogen therapy [40]. This may be important since DXA-derived measurements of geometry by HSA assumes a constant tissue mineralization. Thus, a net gain in mineralization with CaD may cause an overestimate in cross sectional surface. This might suggest that the reported effect of CaD on CSA is actually more modest than suggested by the data in this study.

Hip fractures are more common with advancing age. In the WHI CaD trial, there was a significant interaction of age with CaD, and in women over 60 years, there was a 21% decrease in the risk of hip fractures with CaD. In contrast however, there was no significant interaction of age and CaD on HSA geometry suggesting that CaD has similar effects on bone strength for both older and younger postmenopausal women [29].

One cannot exclude that the effect of CaD on hip structure might be more pronounced in a more calcium-deficient population and this study examined the effects of CaD in postmenopausal women who had an average daily calcium intake, prior to randomization that was close to calcium replete. The lack of any significant interaction of the CaD effect with baseline calcium intake on changes in hip structural geometry however does not support this hypothesis. These results are also consistent with cross-sectional data that demonstrate little effect of calcium intake on any of the HSA structural variables [41].

Significant fracture reduction was found in the main CaD trial among the participants adherent to study treatment. Our analyses similarly demonstrate slightly stronger CaD treatment effects among the adherent women. The importance of the observation that the increase was more pronounced at the intertrochanteric and shaft regions, compared to the narrow neck is unknown.

Strengths and Limitations

This study is the first prospective examination of CaD on hip strength in a multiethnic population of postmenopausal women. Strengths of the study include the longitudinal CaD intervention and serial BMD measurements over several years that allowed assessment for the hip geometric structure changes across time. In addition, the large sample size and carefully defined risk factors for fracture allowed for focused analyses to explore sub-groups of women, based on age, baseline CaD intake or adherence who might demonstrate a greater impact of CaD on hip structure.

There are however some limitations to the study. The HSA method is not the most precise structural measurement, and several limitations have been noted including the precision of estimating 3-dimensional structures from a 2-dimensional measurement and uncertainties in consistent positioning of the femur [42]. One should also be cautious in differentiating between an effect that is not occurring and one that is occurring below the threshold of detectability. This could possibly explain the lack of interaction by age, which was seen in the main CaD and fracture study.

Other limitations include differences in the study population between the main CaD study. DXA scans were only performed in the sub-cohort of women participating in the BMD centers, so the balance in baseline characteristics between the placebo and CaD intervention groups was not completely maintained between studies. Also, the study participants in the CaD trial were at low clinical risk for fracture [7, 32], and these factors may be responsible for the low CaD effect seen on changes in hip structure.

Finally, there were significant differences in baseline BMD and several other HSA parameters between the placebo and the CaD supplementation group at baseline. However, these differences were taken into account when computing the average effects of CaD on bone strength in the longitudinal modeling by adjusting for the baseline parameter. We observed an increased bone strength in both the placebo and the CaD supplement group from baseline to the third year visit of the follow-up, although the increase was much larger in the supplement group in comparison to the placebo group. There are no ready explanations for this increase in bone strength for the placebo group in the first three years of the CaD trial. However, this pattern of change in bone strength did not affect our ability to assess CaD effects at each visit or over the entire trial period since the relative differences between the placebo and the CaD supplementation are the focus of this analysis.

CONCLUSIONS

In summary, participants in the WHI CaD trial were healthy postmenopausal women with few risk factors for fracture who were close to being calcium replete at randomization into the trial. Yet, despite this, CaD supplementation is associated with modest beneficial effects on hip structural features at the femoral narrow neck. These data support a hypothesis that some of the benefit of CaD in reducing hip fracture risk may result from enhanced geometric properties that lead to improved bone strength.

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SHORT LIST OF WHI INVESTIGATORS

Program Office: (National Heart, Lung, and Blood Institute, Bethesda, Maryland) Elizabeth Nabel, Jacques Rossouw, Shari Ludlam, Linda Pottern, Joan McGowan, Leslie Ford, and Nancy Geller.

Clinical Coordinating Center: (Fred Hutchinson Cancer Research Center, Seattle, WA). Ross Prentice, Garnet Anderson, Andrea LaCroix, Charles L. Kooperberg, Ruth E. Patterson, Anne McTiernan; (Wake Forest University School of Medicine, Winston-Salem, NC) Sally Shumaker; (Medical Research Labs, Highland Heights, KY) Evan Stein; (University of California at San Francisco, San Francisco, CA) Steven Cummings.

Clinical Centers: (Albert Einstein College of Medicine, Bronx, NY) Sylvia Wassertheil-Smoller; (Baylor College of Medicine, Houston, TX) Aleksandar Rajkovic; (Brigham and Women's Hospital, Harvard Medical School, Boston, MA) JoAnn Manson; (Brown University, Providence, RI) Annlouise R. Assaf; (Emory University, Atlanta, GA) Lawrence Phillips; (Fred Hutchinson Cancer Research Center, Seattle, WA) Shirley Beresford; (George Washington University Medical Center, Washington, DC) Judith Hsia; (Los Angeles Biomedical Research Institute at Harbor—UCLA Medical Center, Torrance, CA) Rowan Chlebowski; (Kaiser Permanente Center for Health Research, Portland, OR) Evelyn Whitlock; (Kaiser Permanente Division of Research, Oakland, CA) Bette Caan; (Medical College of Wisconsin, Milwaukee, WI) Jane Morley Kotchen; (MedStar Research Institute/Howard University, Washington, DC) Barbara V. Howard; (Northwestern University, Chicago/Evanston, IL) Linda Van Horn; (Rush Medical Center, Chicago, IL) Henry Black; (Stanford Prevention Research Center, Stanford, CA) Marcia L. Stefanick; (State University of New York at Stony Brook, Stony Brook, NY) Dorothy Lane; (The Ohio State University, Columbus, OH) Rebecca Jackson; (University of Alabama at Birmingham, Birmingham, AL) Cora E. Lewis; (University of Arizona, Tucson/Phoenix, AZ) Tamsen Bassford; (University at Buffalo, Buffalo, NY) Jean Wactawski-Wende; (University of California at Davis, Sacramento, CA) John Robbins; (University of California at Irvine, CA) F. Allan Hubbell; (University of California at Los Angeles, Los Angeles, CA) Lauren Nathan; (University of California at San Diego, LaJolla/Chula Vista, CA) Robert D. Langer; (University of Cincinnati, Cincinnati, OH) Margery Gass; (University of Florida, Gainesville/Jacksonville, FL) Marian Limacher; (University of Hawaii, Honolulu, HI) David Curb; (University of Iowa, Iowa City/Davenport, IA) Robert Wallace; (University of Massachusetts/Fallon Clinic, Worcester, MA) Judith Ockene; (University of Medicine and Dentistry of New Jersey, Newark, NJ) Norman Lasser; (University of Miami, Miami, FL) Mary Jo O'Sullivan; (University of Minnesota, Minneapolis, MN) Karen Margolis; (University of Nevada, Reno, NV) Robert Brunner; (University of North Carolina, Chapel Hill, NC) Gerardo Heiss; (University of Pittsburgh, Pittsburgh, PA) Lewis Kuller; (University of Tennessee, Memphis, TN) Karen C. Johnson; (University of Texas Health Science Center, San Antonio, TX) Robert Brzyski; (University of Wisconsin, Madison, WI)

Gloria E. Sarto; (Wake Forest University School of Medicine, Winston-Salem, NC) Mara Vitolins; (Wayne State University School of Medicine/Hutzel Hospital, Detroit, MI) Susan Hendrix.

Figure 1. Calcium and Vitamin D Supplementation Effect by Region and Structural Parameter

* CaD effect found by subtracting the six year percent difference of the placebo group from the intervention group [CaD effect = $(((\text{year 6-baseline}/\text{baseline})*100)_{\text{intervention}} - (((\text{year 6-baseline}/\text{baseline}))*100)_{\text{placebo}}]$.

** Linear regression was used to test the significance of the CaD effect.

Figure 2. Normalized Longitudinal Effect of CaD Intervention on Narrow Neck BMD and Geometric Parameters

Abbreviations: BMD = Bone Mineral Density; CSA = Cross Sectional Area; OD = Outer Diameter; SM = Section Modulus; BR = Buckling Ratio

*p-value = significance of CaD intervention in REM after adjusting for time, baseline parameter, height, and weight

**Year 3 and 6 values were predicted from the model using the baseline population height and weight; and the individual's baseline BMD or geometry measurement.

***Normalized values found by dividing the predicted values for years 3 and 6 by the baseline value

Table 1

Baseline Characteristics by Calcium & Vitamin D Intervention Group

	Placebo (n=979)		CaD (n=991)		p-value ^a
	N	%	N	%	
Age (years)					0.990
50–59	397	40.6%	405	40.9%	
60–69	415	42.4%	418	42.2%	
70–79	167	17.1%	168	17.0%	
Ethnicity					0.262
White (not of Hispanic Origin)	810	82.8	793	80.1	
Hispanic/Latino	41	4.2	50	5.1	
Black/African American	116	11.9	131	13.2	
Asian/Pacific Islander	0	0.0	4	0.4	
American Indian/Alaskan Native	8	0.8	7	0.7	
Other	3	0.3	5	0.5	
Body Mass Index (kg/m²)					0.154
24.9	272	27.8	242	24.4	
25.0 – 29.9	367	37.6	365	36.8	
30.0 – 34.9	221	22.6	227	22.9	
35.0 – 39.9	82	8.4	114	11.5	
40	34	3.5	43	4.3	
Hormone Trial					0.810
Not randomized	539	55.21%	548	55.3%	
Placebo	214	21.9	225	22.7	
Intervention	226	23.1	218	22.0	
Dietary Modification Trial					0.592
Not randomized	284	29.0	302	30.5	
Intervention	251	25.6	262	26.4	
Control	444	45.4	427	43.1	
History of Osteoporosis					0.276
No	912	94.8	924	95.9	

	Placebo (n=979)		CaD (n=991)		p-value ^d
	N	%	N	%	
Yes	50	5.2	40	4.1	
Fracture at age 55+					0.322
No	477	83.8%	483	85.9%	
Yes	92	16.2%	79	14.1%	
Hip Fracture age 55+					0.337
No	529	99.4	509	99.8	
Yes	3	0.6	1	0.2	
Smoking Status					0.530
Never smoked	546	56.4	566	58.1	
Past smoker	338	34.9	336	34.5	
Current smoker	84	8.7	72	7.4	
Self-reported HT Usage					0.514
Never used	488	49.9	497	50.2	
Past user	171	17.5	189	19.1	
Current user	320	32.7	304	30.7	
	Mean	SD	Mean	SD	p-value ^d
Days since CT randomization	426.44	126.79	435.61	136.46	0.122
Years Since Menopause	15.94	9.78	15.53	9.25	0.454
Dietary Energy (kcal)	1777	780.1	1793	826.1	0.670
Total Calcium (mg)	1049	625.7	1039	635.1	0.726
Total Vitamin D (mcg)	7.54	6.36	7.42	5.84	0.640
Total Energy Expended (METS)	10.20	12.74	9.30	11.70	0.164
Body Composition					
Height (cm)	161.8	6.45	161.9	6.04	0.521
Weight (kg)	74.88	15.07	76.46	15.31	0.021
Whole Body BMD	1.01	0.10	1.02	0.11	0.067
Hip BMD	0.86	0.14	0.87	0.13	0.010
Spine BMD	0.98	0.16	0.99	0.16	0.080
Whole Body Mass (kg)	73.74	14.71	75.02	14.81	0.063

	Mean	SD	Mean	SD	p-value ^a
Whole Body Lean Mass (kg)	38.12	5.27	38.70	5.15	0.018
Whole Body Fat Mass (kg)	33.54	10.95	34.22	11.02	0.190
Percent Lean Mass	52.63	6.75	52.51	6.48	0.701
Percent Fat Mass	44.51	7.02	44.64	6.75	0.696

^a p-values represent difference between the placebo and CaD intervention group. T-test were used for continuous variables; Chi-squared test were used for categorical variables

Table 2

Mean (SD) Hip Strength Parameters by CaD Treatment over the Study Period

	Baseline			Year 3			Year 6		
	Placebo (n=963)	CaD (n=971)	p-value	Placebo (n=898)	CaD (n=901)	p-value	Placebo (n=751)	CaD (n=777)	p-value
Narrow Neck									
BMD	0.723	0.736	0.029	0.733	0.750	0.001	0.722	0.742	0.004
(g/cm ²)	(0.131)	(0.129)		(0.136)	(0.134)		(0.136)	(0.133)	
CSA	2.076	2.108	0.061	2.114	2.150	0.047	2.088	2.144	0.006
(cm ²)	(0.372)	(0.366)		(0.385)	(0.382)		(0.393)	(0.391)	
OD	3.023	3.015	0.359	3.038	3.021	0.089	3.047	3.041	0.625
(cm)	(0.203)	(0.209)		(0.212)	(0.214)		(0.228)	(0.229)	
SM	0.931	0.944	0.107	0.959	0.979	0.045	0.952	0.976	0.026
(cm ³)	(0.195)	(0.193)		(0.206)	(0.209)		(0.214)	(0.212)	
BR	12.360	12.060	0.015	12.280	11.870	0.002	12.560	12.130	0.004
	(2.761)	(2.678)		(2.833)	(2.672)		(2.961)	(2.773)	
Intertrochanteric									
BMD	0.725	0.746	<0.001	0.736	0.753	0.012	0.725	0.749	<0.001
(g/cm ²)	(0.134)	(0.136)		(0.139)	(0.135)		(0.137)	(0.135)	
CSA	3.535	3.618	0.002	3.611	3.676	0.047	3.557	3.668	0.002
(cm ²)	(0.668)	(0.654)		(0.670)	(0.669)		(0.691)	(0.667)	
OD	5.114	5.109	0.767	5.154	5.134	0.216	5.162	5.153	0.602
(cm)	(0.348)	(0.359)		(0.330)	(0.321)		(0.347)	(0.319)	
SM	2.936	2.998	0.031	3.026	3.064	0.220	2.987	3.071	0.012
(cm ³)	(0.641)	(0.616)		(0.662)	(0.624)		(0.654)	(0.626)	
BR	10.220	9.919	0.004	10.090	9.826	0.018	10.290	9.904	0.001
	(2.223)	(2.195)		(2.243)	(2.176)		(2.312)	(2.149)	
Shaft									
BMD	1.155	1.180	0.003	1.188	1.206	0.058	1.165	1.199	<0.001
(g/cm ²)	(0.181)	(0.181)		(0.193)	(0.190)		(0.190)	(0.189)	
CSA	3.135	3.203	0.003	3.227	3.278	0.045	3.161	3.257	<0.001
(cm ²)	(0.503)	(0.506)		(0.532)	(0.526)*		(0.522)	(0.527)	
OD	2.856	2.857	0.890	2.857	2.860	0.677	2.856	2.857	0.949

	Baseline		Year 3		Year 6	
	Placebo (n=963)	CaD (n=971)	p-value	Placebo (n=898)	CaD (n=901)	p-value
				Placebo (n=751)	CaD (n=777)	p-value
(cm)	(0.194)	(0.191)		(0.184)	(0.186)	
SM	1.637	1.665	0.045	1.663	1.711	0.003
(cm3)	(0.303)	(0.306)		(0.301)	(0.321)	
BR	3.667	3.576	0.017	3.641	3.509	0.003
	(0.850)	(0.822)		(0.876)	(0.828)	

BMD=Bone Mineral Density, CSA=Cross Sectional Area, OD=Outer Diameter, SM=Section Modulus, CT=Cortical Thickness,
BR=Buckling Ratio

Table 3
Longitudinal Effect of Calcium and Vitamin D Supplementation on BMD and Hip Structural Geometry at the Narrow Neck Region

	Model 1	Model 2
	Coef. (95% CI)	Coef. (95% CI)
BMD (g/cm ²)	0.0074 (0.0027, 0.0121) **	0.0072 (0.0025, 0.0119) **
Outer Diameter (cm)	-0.0065 (-0.0162, 0.0031)	-0.0078 (-0.0174, 0.0019)
Cross-sectional Area (cm ²)	0.0174 (0.0035, 0.0313) *	0.0162 (0.0023, 0.0301) *
Section Modulus (cm ³)	0.0092 (0.0009, 0.0175) *	0.0082 (0.0000, 0.0164) *
Buckling Ratio	-0.1757 (-0.2827, -0.0687) ***	-0.1749 (-0.2820, -0.0678) ***

Model 1: adjusted for baseline measurement for the corresponding variable Model 2: adjusted for corresponding baseline variable, height, and weight

* p 0.05;
** p 0.01;
*** p 0.001
95% CI = 95% confidence interval