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CALCIUM, VITAMIN D SUPPLEMENTATION AND PHYSICAL FUNCTION IN THE WOMEN'S HEALTH INITIATIVE

Robert L. Brunner, PhD¹, Barbara Cochrane, RN, PhD², Rebecca D. Jackson, MD³, Joseph Larson, BA⁴, Cora Lewis, MD, MSPH⁵, Marian Limacher, MD⁶, Milagros Rosal, PhD⁷, Sally Shumaker, PhD⁸, Robert Wallace, MD⁹, and for the WHI Investigators

³Professor, (Rebecca.Jackson@osumc.edu), The Ohio State University Medical Center, 198 McCampbell Hall, 1581 Dodd Dr., Columbus, OH 43201

⁴Statistical Research Associate (jlarson@whi.org), Fred Hutchinson Cancer Research Center, 1100 Fairview Ave. N. PO Box 19024, M3-A410, Seattle WA 98109-1024

⁵Professor, (clewis@mail.dopm.uab.edu) The University of Alabama at Birmingham, Division of Preventive Medicine, 1717 11th Ave., S, 700 Medical Tower Building, Birmingham, AL 35205-4785

⁶Professor, (limacmc@medicine.ufl.edu), Department of Cardiology, University of Florida College of Medicine, Room M-409 Gainesville FL 32610

⁷Associate Professor, (Milagros.Rosal@umassmed.edu), University of Massachusetts Medical School, Preventative and Behavioral Medicine, Worcester, MA 01655, USA

⁸Professor, (sshumake@wfubmc.edu), Department of Public Health Sciences, Wake Forest University School of Medicine, Winston-Salem, NC 27157-1063

⁹Professor, (robert-wallace@uiowa.edu), Department of Epidemiology, University of Iowa, Iowa City, IA 52242

INTRODUCTION

The importance of preserving physical functioning and independence continues to grow in public health because the average life-span of the U.S. population has increased and the percentage of the population in older age categories is growing rapidly (1). Aging is associated with a number of physiological and functional changes that can contribute to increased disability, frailty, falls and fractures, thus lowering quality of life (2, 3). One of the factors that has a strong influence on functional capacity is dietary status (4). The Women's Health Initiative (WHI) showed that calcium and vitamin D supplementation in a randomized trial design resulted in significantly less bone loss at the hip in post-menopausal women given the supplement compared with placebo (5), but whether general physical functioning also improved is not known. The importance of this question is supported by

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¹Corresponding Author: Robert Brunner, Associate Professor, University of Nevada School of Medicine, PMB 251, MS 145, Reno, NV 89557 bbrunner@medicine.nevada.edu; Phone: 775-784-4750; FAX: 775-784-1311. ²Alternate Corresponding Author: Barbara Cochrane RN, PhD. Nurse Scientist, Fred Hutchinson Cancer Research Center, 1100 Fairview Ave. N. PO Box 19024, M3-A410, Seattle WA 98109-1024 and Family and Child Nursing, University of Washington, Seattle, WA 98109-1024 barbc@whi.org; Phone: 206-667-6814; FAX: 206-667-1142.

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studies showing that in women with lower bone mineral density (BMD) there is also poorer physical performance, an important component of physical functioning (6).

Bone health in general and osteoporotic changes in particular are complex and multifactorial with nutritional, genetic and lifestyle determinants and interactions that remain to be comprehensively elucidated (7). A recent review by Heany (8) indicated that among vitamins and minerals, calcium and vitamin D are the most closely related to bone health. Therefore, because average calcium and vitamin D levels in the U.S. are below optimal, supplementation has an important role in bone health to reduce the calcium loss and bone remodeling that are responsible for osteoporotic changes (9).

Very low energy and nutrient intakes are primary nutritional predictors of poorer functional autonomy (10), with low calcium intake, in particular, being implicated in its decline (11). Recent reports have shown that calcium and vitamin D status predicts functional mobility in both community dwelling (12) and home bound elderly subjects (13). Calcium and vitamin D metabolic processes are quite complex, and investigators have proposed both direct and indirect effects of calcium and vitamin D on physical functioning. For example, there are vitamin D receptors contained in both muscle cells and bone (14) such that deficiency may directly affect strength (15) and indirectly affect measures of physical performance (16, 17).

Several studies have demonstrated that lower serum 25(OH)D is related to poorer physical performance (18) and to decreased physical activity (19). Physical activity in turn supports bone maintenance, muscle strength and balance (20, 21), which are important components of physical performance. After menopause the effectiveness of exercise to increase BMD depends on adequate availability of calcium from diet and supplements (22). Older individuals, previously deficient in vitamin D and then supplemented, show significant improvements in muscle strength and physical performance with most improvement in subjects assigned physical training (23). There is also evidence, in women, of a modest association between several measures of bone mineral density and self-reported general physical functioning (24).

Given the relationships among physical activity, physical performance, functional status and quality of life, the additional evidence that calcium and vitamin D supplementation increases bone and muscle strength and activity levels offers compelling rationale to support the current study. Its purpose was to examine the effects of calcium and vitamin D supplementation on various aspects of physical functioning and physical activity. The Women's Health Initiative Calcium and Vitamin D trial (CaD) provided an unique opportunity to prospectively study the effects of CaD supplementation on both subjective and objective measures of physical functioning, as well as subjectively reported physical activity, physical limitations, vitality, bodily pain, and activities of daily living. In order to fully understand study findings, we also investigated the interaction of CaD treatment and baseline calcium intake (i.e., before CaD trial randomization) and treatment and fracture risk level as potential modifiers of CaD effects on both subjective and objective measures of physical functioning.

METHODS

Subjects

The eligibility criteria, recruitment procedures and primary findings for the Women's Health Initiative CaD trial have been published (25, 26). Briefly, women (50–79 years old) were randomized to one or both of the WHI hormone therapy (HT) and dietary modification (DM) trials at 40 U.S. centers between 1993 and 1998. These participants were invited at their first or second annual follow-up visit to join the CaD trial, with 36,282 (53.3%) eligible

and interested participants being subsequently enrolled. To ensure consistency in time intervals between CaD trial enrollment and follow-up measures, only the 33,067 women who joined at the first annual visit (91% of the CaD trial sample) were included in the current analysis (fig. 1). Among subjects in the CaD trial, 31.1% (10,275) were also in HT only, 54.9% (18,150) in DM only and 14.0% (4642) were in both the HT and DM trials. Informed consent was obtained separately for each of the trials, using forms approved by local institutional review boards (IRBs).

Procedures

The CaD trial was a randomized, double-blind and placebo-controlled (5) clinical trial of 1000mg of calcium carbonate plus 400 IU of vitamin D₃ or matching placebo in a regimen of two pills per day (study pills provided by Glaxo SmithKline, Bensalem, PA). After Oct. 1997 a “swallow-able” pill was added to the chewable pill, and both options were offered to all subjects throughout the remainder of the trial. A total of 43.3% of the participants switched study pill types (chewable vs. swallowable) at some point during the study, with 46.0% switching at least once in the active CaD group and 40.5% switching at least once in the placebo group).

Adherence was assessed at least annually from the weight of remaining pills along with a structured interview. Adherence below 80% triggered efforts to optimize adherence with monthly re-evaluations as needed to help with side-effects or other issues.

Questionnaires—Physical functioning was assessed in questionnaires that were collected for all subjects at initial enrollment in WHI (one year prior to CaD trial randomization) and again at the study end (close-out), an average of 7.1 years later. These self-report items had specific relevance to physical functioning i.e. the range of activities the individual can or cannot carry out. These examined domains are consistent with those suggested by the World Health Organization in their International Classification of Functioning, Disability and Health (27). Several relevant (28, 29) sub-scales from the SF-36, a well-established standardized questionnaire, were analyzed all being scored 0 to 100 with a higher score indicating a more favorable state of health. The SF-36 domains included: 1) General Health (5 items), a sub-scale assessing quality of life in regards to one’s general health. 2) Physical functioning (9 items), a sub-scale assessing quality of life in regards to ability to function physically. 3) Role limitations physical (4 items), which assessed quality of life in regard to limitations due to physical health problems. 4) Vitality, energy, fatigue (4 items) which assessed quality of life with regard to energy/fatigue. 5) Bodily pain and stiffness (2 items), assessing quality of life with regard to pain and stiffness.

The reported level of functional independence (no, not limited at all; yes, limited a little; yes, limited a lot) or “activities of daily living” derived from four items describing bathing, dressing, eating and getting in/out of bed. These were totaled as a single variable.

Recreational physical activity was quantified as a continuous variable in METS (ratio of metabolic rate during the activity to the resting metabolic rate) per week using a validated questionnaire (30) and published database of physical activities and MET intensities (31). The construction of composite physical activity variables from items providing examples of activities representing various intensity levels has been described in detail (32). The computed variables were: MET-hours per week (kcal/week per kg) energy expenditure from walking (more than 10 minutes without stopping); expenditure of energy (kcal/week*kg) from mild (low intensity) exercise (e.g. slow dancing, bowling etc.); expenditure of energy (kcal/week*kg) from moderate exercise (e.g. biking outdoors, using an exercise machine etc.); expenditure of energy (kcal/week*kg) from hard exercise (e.g. aerobics, swimming laps etc.); total recreational physical activity per week (MET level for the activity multiplied

by the number of hours exercised per week and summing values for all the types of activities). The assigned MET values for strenuous-, moderate- and low-intensity activities were 7, 4, and 3 METS, respectively. For mean speed of walking (average [2–3mph], fast [3–4 mph] and very fast [>4 mph]), the assigned MET values were 3, 4 and 4.5 respectively. In addition, minutes per week of moderate or strenuous recreational activity were calculated to include walking fairly fast or very fast and participating in activities such as jogging, aerobics, swimming.

Physical clinical data—A random sub-sample (N = 3137) of subjects had three objective physical function measures made at WHI baseline and again 3 and 6 years later (2 years and 5 years after CaD trial enrollment). For grip strength (Jamar™ hand dynamometer, Lafayette Instruments, Lafayette, IN), two measurements were made in the dominant hand with staff coaching for maximal performance. Measures were recorded to the nearest kilogram, rounded up. The chair-stand test was conducted if the subject was able to stand at least once without using hands/arms from a straight-backed, non-padded, flat seated, armless chair. Two 15-second trials of repeated chair stands were performed with arms folded across the chest with a 1- to 2- minute rest in between trials. Chair stands were counted as the participant arose, and counts for both trials recorded. The timed walk utilized a course marked on the floor with end lines 6 meters apart and “X’s” marked just beyond each end line. Participants used ambulatory aids as needed, walking at usual speed to one “X” with a second trial performed to the other “X”. The result was recorded as number of seconds (to nearest one-tenth second) from start to when a foot completely crossed the end line.

Statistical Methods

Baseline measures and change from baseline were calculated as means and standard deviations for the both the active CaD and placebo groups and means and standard errors for differences between the two treatment arms. The effects of CaD on the sixteen physical function measures were tested in linear models, with the variable of interest as a function of CaD treatment assignment. In addition to the main models, interaction models evaluated the relationship between CaD and baseline total calcium intake as well as the relationship between CaD and fracture risk score on physical function. A linear model was developed for each of the sixteen outcome measures with both CaD treatment assignment and the baseline covariate of interest, as well as the interaction between the two. All models were adjusted for WHI trial treatment assignment in the HT and DM trials (i.e. active drug or placebo; low-fat diet intervention or usual diet respectively) and age as a continuous variable. To look at the effects of CaD over time, a series of longitudinal models were also run for the physical function and physical activity variables (those with more than one measurement after baseline), again modeling the effect of interest as a function of CaD treatment assignment.

All subjects were also enrolled in at least one of the other WHI clinical trials (HT, DM). Therefore, all statistical models were adjusted for the other WHI trial treatment assignments and age as a continuous variable. A fracture risk score (scale 0 to 9; mean = 2.3, standard deviation = 1.1) was computed. The nine risk factors making up the scale included: Age 70; Asian or White ethnicity; current smoker; history of any fracture; never used hormones; total calcium intake < 600 mg; history of 2 or more falls in past year; weight < 127 lb; relative who broke bone before age 40. The first 4 of these were collected at initial WHI screening and the last 5 were based on all data available up until CaD trial randomization. Participants with non-missing values for at least 6 of the 9 criteria were included in the analysis. Those with less than 6 non- missing factors had their value for fracture risk set to missing.

To address the issue of multiple comparisons, criteria for statistical significance were adjusted using a Bonferroni method correction for both the main effects ($\alpha = 0.003$ [$0.05/16 \sim 0.003$]) and interaction models ($\alpha = 0.0016$ [$0.05/(16 \times 2)$]). This correction was reflected in all p-values designated as statistically significant. All analyses were completed with SAS version 9.1 (SAS Institute Inc., Cary, NC).

RESULTS

The primary findings are shown in Tables 1 and 2. Baseline (one year prior to CaD trial randomization) and Close-out (end of study) scores for each measure are given for the active CaD and placebo groups. The three far-right columns show CaD versus placebo differences and probability levels. In all cases improvement in function (or mitigation of anticipated decline with aging) is indicated as a positive difference between CaD and placebo (i.e. a CaD benefit). P-values refer to tests of differences between CaD and placebo from baseline to follow-up. At follow-up, the women had generally declined on most physical function and physical activity measures with self-reported exercise tending to be higher at follow-up compared to baseline. Three comparisons reached a “traditional” (uncorrected) level of probability ($p < .05$) with two favoring CaD (year 6 timed walk and minutes of hard exercise) and one favoring placebo (number of activities of daily living adversely affected). The more conservative p-value criterion ($p < .003$), adjusting for multiple comparisons, did not yield any significant differences. To be more certain that significant findings were not overlooked, a repeated measures ANOVA was also done with essentially identical results.

The CaD and placebo groups were compared in linear regression models with interaction terms of total baseline calcium intake (from diet, supplements and medications) first and then fracture risk score, with each specific physical function variable as a response. These models also had the main effects of CaD treatment assignment and variable of interest adjusted for HT treatment assignment, DM treatment assignment and age. Neither of the interactions with calcium intake or fracture risk score had a significant impact on the results, indicating that the effect of CaD supplementation did not significantly change for different levels of baseline calcium intake or fracture risk. (p-value $> .02$ for all interactions).

Only those women who were at least 80% adherent to study pills were examined in a subgroup analysis (data not shown). No significant differences in physical functioning related to treatment assignment were found, similar to results for the entire cohort.

DISCUSSION

Analyses of the WHI randomized controlled trial of calcium and vitamin D supplementation showed no evidence of treatment effects on measures of physical functioning or physical activity. Neither self-reported nor objective measures suggested that CaD treatment produced an improvement or mitigated the decline in physical functioning over time. This conclusion was unchanged after controlling for age and treatment arm in the parallel trials (HT and DM). Also, analyses of subjects who were highly (> 80%) adherent to the treatment did not alter the main results. These latter analyses were important because women adherent to the active CaD regimen were shown to have reduced hip fractures (5). This finding counters possible criticisms of the dose being too low by demonstrating that the treatment was biologically active and effective.

Regardless of treatment assignment, there was a decline in physical functioning (not unexpected in this older cohort) between baseline and follow-up time points (3, 6 and 7 years later) for most measures, whether self-reported or objective. Thus the measures were

sufficiently sensitive to demonstrate a change in physical functioning with age, despite being unaffected by supplemental CaD.

There were some reasons to expect from past work and from known physiologic mechanisms that CaD treatment, especially in adherent women, would have a positive effect. The active CaD dose was shown to be effective in reducing bone loss and fractures, even though women were not selected because of restrictions of activity level, poor nutritional adequacy or other background risk issues such as genetics or inadequate sun exposure (33). It is important to recognize that CaD supplementation reduced falls in women in very high risk categories (34), but improved functioning has not been demonstrated in healthier post-menopausal women (35). Some published data argue against the idea that improving bone health alone should lead to fewer physical limitations in healthy women. For example, neither hormone therapy nor alendronate, potent inhibitors of bone loss have been shown to affect age-related declines in physical functioning (36, 37). Also, only low serum vitamin D levels ($< 20\text{ng/ml}$) were associated with current and declining physical performance levels (38). The physical performance of subjects in the present study did decline over time. However, in this sample, which was not selected for low vitamin D levels, there may still have been insufficient power to detect mitigation of physical function deficits. Arguing against possible insufficient power was our analysis of women at higher risk of fracture (i.e. with low baseline intake of calcium and vitamin D, family history etc.), which showed no treatment benefit for physical functioning. Strengths of this study were its range of measures, both subjective and objective, none of which suggested improvement with active treatment. Potential limitations included the length of treatment, age at which treatment was started, healthy status of the cohort (including relatively few women clearly deficient in calcium or vitamin D) and dosages used.

CONCLUSIONS AND APPLICATIONS

This is the first long-term randomized trial to examine whether supplementing calcium and vitamin D protects against decline of physical functioning in community dwelling older women; the results did not support benefit. Since the level of vitamin D supplementation, which was considered adequate at the time this trial began, is now considered low, caution is warranted in statements about potential efficacy of vitamin D in maintaining or improving physical function. This study included relatively healthy women, and the conclusion of lack of benefit should not be extended to higher risk groups. Nevertheless, consideration of the level of calcium and vitamin D intake at baseline did not change the conclusion that supplementation did not improve physical functioning measures. In future studies, additional sensitive and comprehensive measures of physical function should be considered. Also, it will be important to further examine the relationship between baseline vitamin D blood levels and the effectiveness of CaD supplementation for improving physical function.

Helping individuals to develop clear expectations of the effects of calcium and vitamin D, when they are considering dietary or supplemental intake, is consistent with the role of dietitians in any practice setting. This study, in the context of the rapidly growing number of published reports in the scientific and lay literature on purported health effects of calcium and vitamin D highlights the importance for the dietitian to be knowledgeable of the complex relationships among dietary intake, supplementation, and physiological effects of calcium and vitamin D, as well as the evidence base for their effect on health and physical functioning.

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Figure 1.

Profile of the Calcium with Vitamin D Trial of the Women's Health Initiative. The number of participants tested or completing questionnaires at each time point are shown.

Baseline Self-Reported and Objective Measures of Physical Function and Physical Activity in Women Randomized to Calcium and Vitamin D (CaD) or to Placebo

Table 1

Variable	CaD			Placebo			Difference ¹ (CaD – Placebo)		
	n	Mean	SD	n	Mean	SD	Mean	SE	P
Physical Function (self-report)									
General Health	16549	75.98	16.90	16475	75.83	17.02	0.15	0.19	0.394
Physical Functioning	16529	81.57	20.07	16452	81.36	20.33	0.21	0.22	0.398
Role Limitation Physical	16550	76.16	34.54	16480	75.96	34.68	0.20	0.38	0.635
Vitality (Energy/Fatigue)	16545	64.71	19.44	16470	64.59	19.57	0.12	0.21	0.563
Bodily Pain/Stiffness	16564	74.83	23.00	16489	74.98	23.20	-0.15	0.25	0.577
Activities of Daily Living	16462	4.03	0.26	16397	4.03	0.29	-0.003	0.003	0.308
Incontinence	13088	8.81	2.48	13047	8.83	2.51	-0.02	0.03	0.609
Physical Function (objective)									
Grip Strength, kg	1511	22.81	5.78	1417	22.96	5.75	-0.15	0.21	0.630
Chair Stands	1476	6.52	1.87	1391	6.63	1.82	-0.11	0.07	0.185
Timed Walk, seconds	1507	6.50	5.51	1414	6.19	4.64	0.30	0.19	0.114
Physical Activity² (self-report)									
Walking	15545	4.16	5.67	15493	4.16	5.67	-0.001	0.06	0.940
Mild Exercise	15545	1.39	3.21	15493	1.31	3.09	0.08	0.04	0.028
Moderate Exercise	15545	2.70	4.95	15493	2.68	4.88	0.02	0.06	0.703
Hard Exercise	15545	2.97	7.41	15493	2.93	7.20	0.05	0.08	0.612
Minutes of Recreational Exercise	15545	166.94	176.83	15493	163.99	171.16	2.95	1.98	0.150
Total energy expenditure from recreational activity	15545	11.22	13.21	15493	11.07	12.81	0.15	0.15	0.351

¹ Difference statistics displayed include the differences between the two means (CaD-Placebo) and their corresponding standard errors. P-values are from linear regression analyses modeling the physical function or physical activity measure of interest as a function of CaD treatment assignment, adjusted for age and other WHI trial treatment interventions.

² All METS except as otherwise labeled

Table 2

Change from Baseline to Follow-up¹ in Self-Reported and Objective Physical Function and Physical Activity Measures in Women Supplemented with Calcium and Vitamin D (CaD) Compared to Placebo

Variable	CaD			Placebo			Difference ² (CaD – Placebo)		
	N	Mean	S.D.	N	Mean	S.D.	Mean	S.E.	P-value
Physical Function (self-report)³									
General Health	14019	-6.00	15.98	13895	-6.00	15.85	-0.01	0.19	0.828
Physical Functioning	13732	-10.11	19.96	13566	-9.97	19.83	-0.13	0.24	0.390
Role Limitation Physical	14080	-14.20	41.19	13964	-14.58	41.85	0.38	0.50	0.573
Vitality (Energy/Fatigue)	14013	-4.28	17.72	13898	-4.37	18.03	0.08	0.21	0.890
Bodily Pain/Stiffness	14244	-7.04	25.07	14114	-7.30	24.77	0.27	0.30	0.463
Activities of Daily Living	14134	0.04	0.48	13999	0.03	0.47	0.01	0.01	0.017
Incontinence	9494	0.52	2.25	9417	0.53	2.27	-0.01	0.03	0.921
Physical Function (objective)									
Grip Strength, kg (Year 2)	1334	-1.20	5.63	1265	-1.27	5.30	0.06	0.21	0.790
Grip Strength, kg (Year 5)	1185	-2.49	5.81	1162	-2.64	5.69	0.15	0.24	0.524
Chair Stands (Year 2)	1250	-0.09	1.55	1188	-0.12	1.60	0.03	0.06	0.623
Chair Stands (Year 5)	1065	-0.38	1.81	1053	-0.43	1.81	0.04	0.08	0.603
Timed Walk, seconds (Year 2)	1298	0.11	7.08	1238	0.23	6.38	-0.12	0.27	0.580
Timed Walk, seconds (Year 5)	1160	0.26	6.28	1141	0.81	6.43	-0.54	0.26	0.030
Physical Activity (self-report)⁴									
Walking (Year 2)	14626	-0.10	5.21	14559	-0.12	5.07	0.03	0.06	0.656
Walking (Year 5)	14343	-0.35	5.57	14303	-0.32	5.70	-0.03	0.07	0.634
Mild Exercise (Year 2)	14626	0.11	3.67	14559	0.18	3.64	-0.07	0.04	0.095
Mild Exercise (Year 5)	14343	0.13	3.92	14303	0.10	3.75	0.03	0.05	0.466
Moderate Exercise (Year 2)	14626	0.08	5.61	14559	0.08	5.59	0.01	0.07	0.941
Moderate Exercise (Year 5)	14343	0.23	6.20	14303	0.25	6.15	-0.02	0.07	0.790
Hard Exercise (Year 2)	14626	0.28	7.46	14559	0.20	7.37	0.09	0.09	0.311
Hard Exercise (Year 5)	14343	0.36	8.38	14303	0.17	8.22	0.19	0.10	0.049
Minutes of recreational exercise (Year 2)	14626	4.81	162.24	14559	5.55	158.46	-0.74	1.88	0.690

Variable	CaD			Placebo			Difference ² (CaD – Placebo)		
	N	Mean	S.D.	N	Mean	S.D.	Mean	S.E.	P-value
Minutes of recreational exercise (Year 5)	14343	4.73	177.83	14303	3.54	174.33	1.19	2.08	0.568
Total energy expenditure from recreational activity (Year 2)	14626	0.38	11.81	14559	0.33	11.55	0.05	0.14	0.724
Total energy expenditure from recreational activity (Year 5)	14343	0.38	13.19	14303	0.20	12.95	0.18	0.15	0.255

¹ Change was calculated as the difference between the given follow-up year and baseline. Means and standard deviations were then calculated from this new variable

² Difference statistics displayed include the differences between the two means (CaD-Placebo) and their corresponding standard errors. P-values are from linear regression analyses modeling the physical function or physical activity measure of interest as a function of CaD treatment assignment, adjusted for age and other WHI trial treatment interventions.

³ Follow-up self-reported psychosocial measures were completed at study end (close-out)

⁴ All METS except as otherwise labeled