Muscle Cramps Do Not Improve With Correction of Vitamin D Insufficiency

Madelyn K. Weiker, MD; Birgitte Nielsen; Andrew J. Waclawik; Abigail C. Staples; Karen E. Hansen, MD, MS

ABSTRACT

Background: Minimal treatment options exist for idiopathic muscle cramps.

Objective: We evaluated whether correction of vitamin D insufficiency relieved muscle cramps in postmenopausal women.

Methods: We conducted a post hoc analysis of a randomized, double-blind, placebo-controlled trial at a single academic medical center in the Midwest to evaluate the benefits of treating vitamin D insufficiency. Two hundred thirty postmenopausal women participated. Eligible women were ≤75 years old, 5 years past menopause or oophorectomy, or ≥60 years if they had previously undergone hysterectomy without oophorectomy. Women had vitamin D insufficiency at baseline (25-hydroxyvitamin D 14-27 ng/mL). We excluded subjects with a glomerular filtration rate <45 mL/minute.

Interventions for Clinical Trials: Participants completed food diaries, laboratory studies, and functional tests including the Timed Up and Go test, Physical Activity Scale for the Elderly, Health Assessment Questionnaire (a measure of disability), and pain scores. Subjects recorded muscle cramp frequency and severity using a standardized form at 6 visits over 1 year.

Results: During the trial, over half of participants (n=121, 53%) reported muscle cramps. Despite unequivocal vitamin D repletion, vitamin D had no effect on muscle cramps. Pain levels, disability, and dietary potassium predicted presence of cramps. Serum albumin and physical activity were inversely associated with, and disability was positively associated with, severity of muscle cramps.

Conclusions: Further studies are needed to evaluate the link between pain, disability, dietary potassium intake, and muscle cramps.

Author Affiliations: Department of Medicine, University of Wisconsin-Madison (Weiker, Nielsen, Staples, Hansen); Department of Neurology, University of Wisconsin-Madison (Waclawik).

Corresponding Author: Karen E. Hansen, MD, MS, Department of Medicine, University of Wisconsin-Madison, Room 4124 MFCB, 1685 Highland Ave, Madison, WI 53705-2281; phone 608.263.0517, fax 608.263.7353, e-mail keh@medicine.wisc.edu.

INTRODUCTION

Muscle cramps are defined as "sudden, uncomfortable squeezing or contraction of a muscle, lasting seconds to minutes."[1,2] In surveys,[3-6] between half and two-thirds of older adults experience muscle cramps, contributing to insomnia[6] and lower quality of life.[7] Some people describe muscle soreness or tenderness the following day.[7] Muscle cramps have diverse potential causes including lower motor neuron disorders; cirrhosis; dialysis; medications; and metabolic derangements including hypocalcemia, hypoglycemia, hyponatremia, and abnormal potassium levels.[1,8] However, most muscle cramps are idiopathic.[1]

Multiple interventions are suggested for muscle cramps, but few have proven effective in double-blind, placebo-controlled trials. In 1 clinical trial, stretching prior to bedtime reduced muscle cramp frequency.[9] Quinine moderately reduced frequency and severity of cramps, but its side effect profile prohibits routine use.[10] Other treatments, including vitamin B complex, diltiazem, vitamin E, magnesium, and gabapentin are of uncertain benefit.[2]

Identification of risk factors for muscle cramps might guide future treatment options. During a randomized, double-blind, placebo-controlled trial of vitamin D therapy in postmenopausal women,[11] we asked participants to complete a questionnaire during each of 6 visits over 1 year to assess the presence and severity of cramps as a function of vitamin D therapy. Because hypocalcemia causes tetany, and dialy-sis with disrupted vitamin D metabolism is a risk factor for muscle cramps, we hypothesized that vitamin D would reduce

the frequency and severity of muscle cramps in postmenopausal women with vitamin D insufficiency.

Herein, we report our planned post hoc analysis to evaluate the effect of vitamin D on muscle cramps, including associations between muscle cramps and subjects' clinical features, nutritional habits, total fractional calcium absorption, and functional measures.

METHODS

This study (clinicaltrials.gov NCT00933244) was approved by the University of Wisconsin Human Subjects Committee and all subjects provided written informed consent to participate.

Subjects participated in a single-center, randomized, double-blind, placebo-controlled trial[11] to evaluate the effect of vitamin D therapy on total fractional calcium absorption (TFCA), bone mineral density (BMD), and functional status. Participants were women ≤75 years old, at least 5 years past menopause or oophorectomy, or ≥60 years if they had undergone a prior hysterectomy without oophorectomy. Women had baseline 25-hydroxyvitamin D [25(OH)D] levels of 14 to 27 ng/mL by high performance liquid chromatography. Women were excluded if they had a glomerular filtration rate <45 mL/minute, estimated by the Modification of Diet in Renal Disease (MDRD) equation.[12] Complete exclusion criteria are described elsewhere.[11] During the trial, women were advised to consume 600 to 1400 mg of calcium per day.

To assess the frequency and severity of muscle cramps, subjects completed a questionnaire at each of the 6 study visits over 1 year (Table 1). We developed the questionnaire a priori and assigned point values to each answer, with higher scores indicating more frequent or severe cramps causing greater disturbance to daily activities and/or sleep. We calculated the composite muscle cramp score for each subject, using the sum of points from all 6 visits.

At baseline, all subjects underwent measurement of serum 25(OH)D, calcium, albumin, phosphorus, magnesium, creatinine, parathyroid hormone levels, TFCA, and BMD. Nutritional habits and supplement use were determined from analysis of 4- to 7-day food diaries by a research dietician, using Food Processor software (ESHA Research) prior to randomization. We measured subjects' total fluid intake, 24-hour urine calcium levels, and TFCA the day prior to randomization, as described elsewhere.[11]

We assessed subjects' measures of physical function and pain at each of 6 study visits. Participants completed the Timed Up and Go (TUG) and 5 sit-to-stand (5STS) tests twice per visit, and the final score was the better of 2 attempts. Subjects completed the Physical Activity Survey for the Elderly (PASE), with higher points indicating greater physical activity. Additionally, subjects completed the modified Stanford Health Assessment Questionnaire (HAQ),[13] with a possible score of 0 (no disability) to 3 (unable to perform or requiring assistance). Subjects marked their pain level due to any cause from 0 (no pain) to 10 (severe pain) on a 10 cm horizontal line in response to the question, "How much pain have you had in your muscles and bones in the past week?" We noted subjects' use of medications throughout the trial, including those known to cause or alleviate muscle cramps.

Table 1. Muscle Cramps Questionnaire

Question	Answer	Score
Do you have muscle cramps?	No	0
	Yes	1
If yes, how often?	Once or less a day	0
	2 to 5 times daily	3
	6 or more times daily	4
Do muscle cramps keep you from falling asleep?	No	0
	Yes	1
Do muscle cramps wake you during the night?	No	0
	Yes	1
Total		Range 0 to 7

After initial measurement of TFCA, subjects were randomized to 1 year of placebo, a low-dose vitamin D_3 regimen of 800 IU/day, or a high-dose vitamin D_3 regimen specifically designed to keep the 25(OH)D level >30 ng/mL throughout the trial. All subjects took a daily pill (placebo or 800 IU vitamin D_3) and intermittent yellow pills (placebo or 50,000 IU vitamin D_3 days 1 to 15 then every 15th day) to preserve the double-blind.

The CONSORT guidelines for the clinical trial were published with the parent paper.[11] Of relevance, 230 women were randomized into the trial including 76 assigned to placebo, 75 assigned to low-dose and 79 assigned to high-dose vitamin D therapy. Of the 230 women randomized, 221 women (96%) completed the trial including 73, 74, and 74 in the placebo, low-dose, and high-dose vitamin D arms, respectively.

Statistical Analysis

Data were entered in duplicate and accuracy confirmed prior to analysis. Variables included race and baseline age, height, weight, body mass index, tobacco use, nutrient intake from diet and supplements, laboratory results, TFCA, TUG and 5STS test times, and HAQ, PASE, and pain scores. All data were graphed to determine distributions (parametric or skewed) and then summarized using the mean ± standard deviation or median (interquartile range), as appropriate. We analyzed continuous data using independent t-tests or the Wilcoxon test, and categorical data using the chi-squared test. We used the "leaps" command to evaluate the top predictors of muscle cramps, focusing on the top 17 variables identified in initial analyses. In the subset of women with muscle cramps, we used Spearman correlation coefficients to assess relationships between subjects' characteristics and muscle cramp severity. The Benjamini-Hochberg correction[14] was employed to control the false positive discovery rate during univariate analyses; thus, a P-value ≤0.002 was considered significant. A P-value <0.05

Table 2. Characteristics of Subjects With and Without Muscle Cramps

Characteristic	All Subjects n=230	No Cramps n=109 (47%)	Cramps n=121 (53%)	*P*-Value
Clinical				
Age, years	61 ± 6	61 ± 6	61 ± 6	0.943
BMI, kg/m^2	30.8 ± 6.8	30.2 ± 6.1	31.4 ± 7.5	0.155
Race				
White	207 (90%)	101 (92%)	106 (88%)	
Black	14 (6%)	5 (5%)	9 (7%)	0.469
Other	9 (4%)	3 (3%)	6 (5%)	
Tobacco use	20 (9%)	6 (6%)	14 (12%)	0.158
Daily Nutrient Intake				
Calories, kcal	1,842 (1,539, 2,198)	1,839 (1,487, 2,226)	1,842 (1,572, 2,154)	0.816
Protein, g	75 (62, 86)	76 (63, 87)	74 (61, 86)	0.481
Fat, g	72 (60, 91)	68 (55, 92)	74 (61, 90)	0.327
Carbohydrates, g	222 (175, 266)	226 (179, 278)	209 (175, 259)	0.127
Fiber, g	19 (14, 25)	20 (15, 27)	18 (14, 24)	0.022
All calcium intake, mg	967 (752, 1,215)	1,026 (793, 1,264)	905 (731, 1,152)	0.034
Vitamin D, IU	196 (115, 266)	203 (134, 282)	169 (111, 259)	0.173
Magnesium, mg	306 (247, 370)	309 (251, 383)	301 (237, 356)	0.245
Iron, mg	13 (10, 16)	14 (10, 16)	13 (10, 16)	0.315
Phosphorus, mg	1,300 (1,086, 1,475)	1,318 (1,091, 1,565)	1,283 (1,081, 1,464)	0.412
Potassium, mg	2,775 (2,313, 3,249)	3,018 (2,453, 3,440)	2,665 (2,212, 3,053)	0.002
Total fluid intake, mL	2683 (2159, 3350)	2692 (2214, 3326)	2640 (2157, 3449)	0.993
Labs				
Calcium, mg/dL	9.1 ± 0.4	8.9 ± 0.3	8.9 ± 0.3	0.416
Albumin, g/dL	3.9 ± 0.3	3.9 ± 0.3	3.9 ± 0.3	0.813
GFR, mL/minute	79 ± 17	82 ± 17	76 ± 16	0.022
PTH, pg/mL	51 ± 21	51 ± 24	50 ± 17	0.740
25(OH)D, ng/mL	21 ± 3	21 ± 5	19 ± 5.0	0.045
Magnesium, mg/dL	2.1 ± 0.2	2.1 ± 0.2	2.1 ± 0.2	0.998
Phosphate, mg/dL	3.5 ± 0.5	3.4 ± 0.5	3.5 ± 0.4	0.285
1,25(OH)$_2$D, pg/mL	41 (31, 54)	43 (33, 55)	40 (29, 54)	0.131
Estradiol, pg/mL	48 (40, 56)	47 (41, 55)	49 (40, 57)	0.622
24-hour urine calcium, mg	180 ± 95	192 ± 108	167 ± 82	0.043
Calcium absorption	0.20 ± 0.07	0.20 ± 0.07	0.21 ± 0.07	0.467
Function				
Physical Activity Scale	171 ± 88	175 ± 93	166 ± 82	0.442
Timed Up and Go	8.1 ± 1.7	8.0 ± 1.8	8.2 ± 1.6	0.350
5 Sit-to-Stand Test	10 ± 2.7	9.7 ± 2.5	10.3 ± 2.8	0.143
HAQ	0.1 ± 0.3	0.06 ± 0.18	0.15 ± 0.30	0.008
Pain, 10-point scale	1.5 ± 1.9	0.9 ± 1.3	2.1 ± 2.2	<0.001

Abbreviations: BMI, Body Mass Index, GFR, glomeruler filtration rate; PTH, Parathyroid hormone; HAQ, Health Assessment Questionnaire.

Table 3. Medications Influencing Muscle Cramps

Medications Used to Treat Muscle Cramps	Medications Causing Muscle Muscle Cramps
Carisoprodol	Albuterol/ipratropium
Diltiazem	Intravenous iron sucrose
Magnesium	Levalbuterol
Orphenadrine	Pregabalin
Quinine	Selective serotonin reuptake inhibitors
Verapamil	
Vitamin B complex	

was considered significant in multivariate models. We used version 3.2.3 of "R" (The R Project for Statistical Computing, http://www.r-project.org) to perform statistical analyses.

RESULTS

We analyzed baseline data and muscle cramp questionnaires from all 230 subjects who participated in the study. The majority of participants were white (90%) with a mean age of 61 ± 6 years and body mass index of 30.8 ± 6.8 kg/m^2 (Table 2). More than half of subjects (n=121, 53%) reported muscle cramps during the trial. Among those with muscle cramps, the median composite cramp score was 4 (interquartile range 2-8).

High-dose vitamin D resulted in unequivocal vitamin D repletion to serum 25(OH)D levels ≥30 ng/mL throughout the trial.[11] However, vitamin D had no effect on the frequency of muscle cramps, with 32 of 76 subjects in the placebo, 34 of 75 in the low-dose vitamin D, and 31 of 79 subjects in the high-dose vitamin D arms during the trial experiencing muscle cramps (*P*=0.746). Likewise, vitamin D had no effect on muscle cramp severity. The composite cramp score was 3.2 ± 4.7 in the placebo, 3.5 ± 5.4 in the low-dose, and 2.7 ± 3.8 in the high-dose vitamin D arms (*P*=0.927).

Surprisingly, use of medications potentially causing or relieving cramps (Table 3) was similar between subjects with and without cramps. Causative medication use was noted in 18 of 103 women with cramps, and in 8 of 101 without cramps (*P*=0.111). Likewise, 24 of 97 women with cramps, and 18 of 91 women without cramps, took medications believed to alleviate cramps (*P*=0.631).

Women with muscle cramps had significantly higher pain levels (2.1 ± 2.2 vs. 0.9 ± 1.3, *P*<0.001) and consumed less potassium (2,665 mg/day [2,212 mg; 3,053 mg] vs 3,018 mg/day [2,453 mg; 3,440 mg], *P*=0.002) than those without cramps. Women with muscle cramps also reported greater disability (HAQ score 0.15 ± 0.30 vs 0.06 ± 0.18, *P* =0.008), although the *P*-value was above the false-positive discovery rate *P*-value of

0.002. Although clinicians often recommend hydration to treat muscle cramps, we found no significant difference in total fluid intake between women with and without cramps (Table 2).

We used the R program "leaps" to identify which of the top 17 variables from Table 2 predicted presence of muscle cramps. Candidate variables included tobacco use, body mass index, HAQ, pain, serum creatinine, calcium, phosphorus, 25(OH)D, $1,25(OH)_2D$, 24-hour urine calcium, TFCA, and dietary intake of carbohydrates, fiber, calcium, magnesium, potassium, and vitamin D. In this analysis, dietary potassium, serum creatinine, and pain levels were the only significant variables predicting the presence of muscle cramps (Table 4). Together these three variables predicted over 70% of the variability in presence of muscle cramps. Restricting the analysis to 10 or fewer variables did not alter these results.

Among women reporting muscle cramps (n=121), we used correlation coefficients to assess relationships between patient characteristics and the severity of muscle cramps (Table 5). In these analyses, serum albumin and physical activity were inversely associated with, and disability was positively associated with, severity of muscle cramps. Pain also was positively associated with severity of muscle cramps, but the *P*-value was >0.05.

Table 4. Variables Associated With Presence of Muscle Cramps

	Multivariate Model		
Characteristic	**Slope**	**Standard Error**	***P*-value**
Intercept	+0.0947	1.116	0.932
Creatinine, mg/dL	+1.9798	1.0944	0.070
Potassium intake, mg	-0.0007	0.0002	0.001
Pain, 10-point scale	+0.3413	0.0985	<0.001

Full model *P*<0.001, area under the curve = 0.708.

Dietary potassium, serum creatinine, and pain levels were the only significant variables predicting the presence of muscle cramps; they predicted over 70% of the variability in muscle cramps.

Table 5. Correlations Between Characteristics and Severity of Muscle Cramps

	Subjects With Muscle Cramps, n=121	
Characteristic	**ρ**	***P*-value**
Albumin, g/L	-0.19	0.039
Pain, baseline	+0.13	0.169
Pain, cumulative	+0.17	0.067
Health Assessment Questionnaire Score, baseline	+0.19	0.039
Health Assessment Questionnaire Score, cumulative	+0.21	0.026
Physical Activity Scale for the Elderly, baseline	-0.23	0.011
Physical Activity Scale for the Elderly, cumulative	-0.19	0.046

Pain was assessed using a 10-cm visual analog scale. Cumulative scores are the sum of individual scores obtained at each of 6 visits over 1 year. Data are not shown, for variables showing no significant correlation with muscle cramp score.

DISCUSSION

Muscle cramps commonly affect older adults and most cramps are idiopathic in nature. Understanding their pathophysiology could allow identification of new treatments for this common ailment, which is associated with insomnia and lower quality of life.[7] We therefore sought to identify potential novel causes of muscle cramps and were particularly interested in the effect of vitamin D.

In our randomized clinical trial, vitamin D therapy did not alter the frequency or severity of muscle cramps. However, women experiencing muscle cramps had significantly higher pain levels, greater disability by greater HAQ, and consumed less potassium than subjects without cramps. Although magnesium supplements and hydration are commonly suggested to treat muscle cramps, we found no relationship between muscle cramps and dietary or serum magnesium or fluid intake. We found that severity of muscle cramps was inversely associated with serum albumin and physical activity, and positively associated with disability and pain.

Additionally, women with muscle cramps had more pain and disability than those without muscle cramps. We cannot determine whether higher pain levels directly cause muscle cramps. However, consistent with the concept of central sensitization, subjects with higher pain levels might have increased nociceptive sensitivity[15] and therefore be more symptomatic when muscle cramps occur. Cramps might sensitize pain nerve fibers, reducing functional status.

We found that women with muscle cramps consumed less dietary potassium. While hypokalemia is a known cause of muscle cramps, we found no studies in which dietary potassium was identified as a risk factor for cramps. Further research is needed to evaluate whether increased potassium intake would reduce muscle cramps.

We could find no reports linking regular exercise with milder muscle cramps. Although muscle cramps are more common in people with liver disease, we likewise found no reports linking low albumin to greater risk of muscle cramps. However, one review[16] suggested that shifts in plasma volume contributed to muscle cramps in liver disease, which might relate to altered serum albumin levels.

Strengths and Limitations

Our study had a number of strengths. We analyzed a number of subjects' clinical features, nutritional habits, laboratory data, and functional measures. Additionally, our subjects were highly motivated, indicated by low attrition (4%) and excellent adherence to study pills (median ~99% to 100%).[11]

We also acknowledge some weaknesses of this study. First, this was a post hoc analysis of a single-center, randomized, double-blind, placebo-controlled trial focused on changes in TFCA, BMD, and functional status with correction of vitamin D insufficiency,

rather than on muscle cramps. Our study was limited to postmenopausal and mostly white women. Additionally, at the study's onset, we found no validated questionnaires developed to measure muscle cramps so created our own questionnaire. However, others[6] recently validated and published a questionnaire similar to our own. Finally, the observational nature of this study can only suggest, not prove, causes of muscle cramps.

CONCLUSIONS

Muscle cramps are highly prevalent in the general population. Our study provides good evidence that vitamin D does not reduce muscle cramps in postmenopausal women with baseline serum 25(OH)D levels equaling 21±3 ng/mL. In our study, muscle cramps were associated with higher levels of pain and disability and lower potassium intake. Given the high prevalence of muscle cramps and their impact on quality of life, future research is warranted to establish the causes of muscle cramps. Such knowledge could direct double-blind, placebo-controlled trials to identify effective treatments.

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