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 insomnia⁶ 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 dialysis with disrupted vitamin D metabolism is a risk factor for muscle cramps, we hypothesized that vitamin D would reduce

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
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 trial11 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 oopho-
rectomy, 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 liq-
uid chromatography. Women were excluded if they had a glomer-
ular filtration rate <45 mL/minute, estimated by the Modification
of Diet in Renal Disease (MDRD) equation.12 Complete exclu-
sion 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, creati-
ine, 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 During the trial, the subjects took a daily pill (placebo or 800 IU vitamin D3) and intermittent yellow pills (placebo or 50,000 IU vitamin D3) 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 random-
ized 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.

Table 1. Muscle Cramps Questionnaire

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

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 sup-
plements, laboratory results, TFCA, TUG and 5STS test times,
and HAQ, PASE, and pain scores. All data were graphed to deter-
mine distributions (parametric or skewed) and then summarized
using the mean ± standard deviation or median (interquartile
range), as appropriate. We analyzed continuous data using inde-
pendent 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 vari-
hables 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 correction14 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

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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/m² (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<0.001), although the P-value was above the false-positive discovery rate P-value of

### Table 2. Characteristics of Subjects With and Without Muscle Cramps

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Subjects n=230</th>
<th>No Cramps n=109 (47%)</th>
<th>Cramps n=121 (53%)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>61 ± 6</td>
<td>61 ± 6</td>
<td>61 ± 6</td>
<td>0.943</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>30.8 ± 6.8</td>
<td>30.2 ± 6.1</td>
<td>31.4 ± 7.5</td>
<td>0.155</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>207 (90%)</td>
<td>101 (92%)</td>
<td>106 (88%)</td>
<td>0.469</td>
</tr>
<tr>
<td>Black</td>
<td>14 (6%)</td>
<td>5 (5%)</td>
<td>9 (7%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>9 (4%)</td>
<td>3 (3%)</td>
<td>6 (5%)</td>
<td></td>
</tr>
<tr>
<td>Tobacco use</td>
<td>20 (9%)</td>
<td>6 (6%)</td>
<td>14 (12%)</td>
<td>0.158</td>
</tr>
<tr>
<td>Daily Nutrient Intake</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calories, kcal</td>
<td>1,842 (1,539, 2,198)</td>
<td>1,839 (1,487, 2,226)</td>
<td>1,842 (1,572, 2,154)</td>
<td>0.816</td>
</tr>
<tr>
<td>Protein, g</td>
<td>75 (62, 86)</td>
<td>76 (63, 87)</td>
<td>74 (61, 86)</td>
<td>0.481</td>
</tr>
<tr>
<td>Fat, g</td>
<td>72 (60, 91)</td>
<td>68 (65, 92)</td>
<td>74 (61, 90)</td>
<td>0.327</td>
</tr>
<tr>
<td>Carbohydrates, g</td>
<td>222 (175, 266)</td>
<td>226 (179, 278)</td>
<td>209 (175, 259)</td>
<td>0.127</td>
</tr>
<tr>
<td>Fiber, g</td>
<td>19 (14, 25)</td>
<td>20 (15, 27)</td>
<td>18 (14, 24)</td>
<td>0.022</td>
</tr>
<tr>
<td>All calcium intake, mg</td>
<td>967 (752, 1,215)</td>
<td>1026 (793, 1,264)</td>
<td>905 (731, 1,152)</td>
<td>0.034</td>
</tr>
<tr>
<td>Vitamin D, IU</td>
<td>196 (115, 266)</td>
<td>203 (134, 282)</td>
<td>169 (111, 259)</td>
<td>0.173</td>
</tr>
<tr>
<td>Magnesium, mg</td>
<td>306 (247, 370)</td>
<td>309 (251, 383)</td>
<td>301 (237, 356)</td>
<td>0.245</td>
</tr>
<tr>
<td>Iron, mg</td>
<td>13 (10, 16)</td>
<td>14 (10, 16)</td>
<td>13 (10, 16)</td>
<td>0.315</td>
</tr>
<tr>
<td>Phosphorus, mg</td>
<td>1,300 (1,086, 1,475)</td>
<td>1,319 (1,091, 1,565)</td>
<td>1,283 (1,081, 1,146)</td>
<td>0.412</td>
</tr>
<tr>
<td>Potassium, mg</td>
<td>2,775 (2,313, 3,249)</td>
<td>3,018 (2,453, 3,440)</td>
<td>2,665 (2,212, 3,053)</td>
<td>0.002</td>
</tr>
<tr>
<td>Total fluid intake, mL</td>
<td>2683 (2159, 3350)</td>
<td>2692 (2242, 3326)</td>
<td>2640 (2157, 3449)</td>
<td>0.993</td>
</tr>
</tbody>
</table>

### Table 3. Medications Influencing Muscle Cramps

<table>
<thead>
<tr>
<th>Medications Used to Treat Muscle Cramps</th>
<th>Medications Causing Muscle Muscle Cramps</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carisoprodol</td>
<td>Albuterol/pratropium</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>Intravenous iron sucrose</td>
</tr>
<tr>
<td>Magnesium</td>
<td>Levalbuterol</td>
</tr>
<tr>
<td>Orphenadrine</td>
<td>Pregabalin</td>
</tr>
<tr>
<td>Quinine</td>
<td>Selective serotonin reuptake inhibitors</td>
</tr>
<tr>
<td>Verapamil</td>
<td></td>
</tr>
<tr>
<td>Vitamin B complex</td>
<td></td>
</tr>
</tbody>
</table>

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

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 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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REFERENCES
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