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Comparing Vitamin D Supplementation versus Placebo for Urgency Urinary Incontinence: A Pilot Study

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Abstract

Objectives: To estimate the efficacy of vitamin D supplementation to reduce urgency urinary incontinence (UUI) episodes

Design: Pilot, 2-arm, randomized trial conducted from 2013–2017. Interventions were 12 weeks of weekly oral 50,000 IU vitamin D3 or placebo.

Setting: Academic, university-based outpatient clinic

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Authors' Contributions

ADM : study concept and design, data analysis and interpretation, manuscript preparation
TMB : study concept and design, data analysis and interpretation, manuscript preparation
VT : study concept and design, data analysis and interpretation, manuscript preparation
CV : study concept, data analysis and interpretation, manuscript preparation
HER : study concept and design, data analysis and interpretation, manuscript preparation
KLB : study concept and design, data analysis and interpretation, manuscript preparation
PSG : study concept and design, data analysis and interpretation, manuscript preparation

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Conflicts of Interest

ADM : none
TMB : none
VT : none
CV : none
HER : UpToDate, Renovia
KLB : none
PSG : none

Participants: Community-dwelling postmenopausal women, 50 years of age or older, with at least 3 UUI episodes on 7-day bladder diary and serum 25(OH)D ≤ 30 ng/mL

Measurements: The primary efficacy estimate was the percentage change in UUI episodes. Secondary estimates included changes in other lower urinary tract symptoms, along with exploratory subgroup analysis by race/ethnicity and obesity.

Results: We randomized 56 women (50 to 84 years of age; mean= 60.5 ±8.2), 28 to vitamin D and 28 to placebo; 51 completed treatments. Mean serum 25(OH)D at baseline (21.2 ±5.2 and 18.2 ±5.6, p=0.30) improved to 57.9 ±16.3 ng/mL with vitamin D3 and 21.9 ±8.2 ng/mL with placebo, p<0.001. UUI episodes per 24-hour day decreased by 43.0% with vitamin D3 compared to 27.6% with placebo (p=0.22). Among Black women (n=33), UUI episodes decreased by 63.2% with vitamin D3 compared to 22.9% with placebo (p=0.03). Among obese women, UUI episodes decreased by 54.1% with vitamin D compared to 32.7% with placebo (p=0.29). For all women, changes in voiding frequency (p=0.40), nocturia (p= 0.40), urgency (p=0.90), incontinence severity (p=0.81), and overactive bladder symptom severity (p=0.47) were not different between arms.

Conclusions: Post-menopausal women with UUI and vitamin D insufficiency demonstrated a >40% decrease in UUI episodes, which did not reach statistical significance compared to placebo, except in the subset of Black women. The results of this pilot study support further investigation of vitamin D3 alone or in combination with other treatments for UUI, particularly for women in higher-risk subgroups.

Keywords

urgency urinary incontinence; vitamin D insufficiency; vitamin D deficiency; post-menopausal; women; pilot study

INTRODUCTION

Treatment of urgency urinary incontinence (UUI) in older women is multicomponent involving lifestyle, behavioral, and often drug therapy with the potential for adverse events. Identification of novel treatments that maximize the impact of multicomponent therapy and reduce the potential for adverse drug events is needed.

Translational evidence from basic science, epidemiologic research, and small clinical trials provide rationale for the role of vitamin D to reduce UUI. Vitamin D receptors are present in the bladder detrusor and striated muscle and may be potential treatment targets.[1,2] Vitamin D may decrease involuntary urgency sensations and improve UUI via better regulation of stromal and smooth muscle growth; thus, improving detrusor muscle response to bladder filling. Cross-sectional studies show conflicting results with regard to prevalent UI among older women with low serum vitamin 25-hydroxyvitamin D [25(OH)D].[3,4] One longitudinal study found women with higher dietary vitamin D intake had decreased risk of incident overactive bladder (OAB) and UI;[5] whereas, other studies found mixed associations between incident UI and low 25(OH)D levels.[6,7] Separate clinical trials in women reported improvement in UUI with higher vs lower dosages of either vitamin D or a vitamin D analog vs placebo.[8,9]

To explore whether correction of vitamin D deficiency improves UUI symptoms in post-menopausal women, we conducted a pilot randomized, study of vitamin D supplementation in older women with both UUI and vitamin D insufficiency (serum 25(OH)D levels <30 ng/mL).

METHODOLOGY

Study Design

This was a pilot randomized, double-blind, placebo-controlled trial to estimate the effect of vitamin D supplementation for treatment of UUI. The University of Alabama at Birmingham's institutional review board approved the study and all participants signed informed consent. Enrollment occurred January 2013 to May 2017.

Participants

Participants were post-menopausal, community-dwelling women, age ≥50 years, with predominant UUI (≥3.0 episodes per 7-days). Supplemental Table 1 lists inclusion and exclusion criteria. Recruitment occurred through specialty continence care clinics and primary care clinics, public announcements, mailings, and advertisements.

Clinical evaluation consisted of a medical and continence history, physical examination, mental status screening with the Mini-Cog,[10] urinalysis, serum 25(OH)D level, and for participants with diabetes, a glycosylated hemoglobin. Post-void residual (PVR) determination by ultrasound was performed. Participants then completed a 7-day bladder diary. Inclusion required participants to have a 25(OH)D level <30 ng/mL. Serum 25(OH)D levels were measured using the IDS iSYS automated system (Gaithersburg, MD) meeting NIHNIST/NIH Vitamin D Metabolites Quality Assurance Program (VitDQAP) standards for accuracy.[11]

Randomization and Intervention

Using a computer-generated 1:1 allocation ratio, participants were randomized to receive weekly oral 50,000IU vitamin D3 or placebo for 12 weeks (Tishcon, Corp.). All patients and study personnel were blinded to treatment assignment. Participants were seen in clinic for 4 visits: screening, randomization, 6, and 12 weeks.

Descriptive Variables

Descriptive data included self-reported race/ethnicity, current insurance status and current use of tobacco, list of medications, prior UI treatment, prior hysterectomy, and parity. From the medication list, diuretics (loop, thiazide, and potassium-sparing) were identified. The Functional Comorbidity Index was used to measure the number of chronic comorbid diseases.[12] Adiposity status was computed using body mass index (BMI, kg/m2), and classified as non-obese (<29.9) or obese (>30). Waist circumference was measured 2.5 cm above the umbilicus.

Outcome Assessments for Efficacy Estimates

The primary outcome was the percent change in frequency of UUI as documented in the 7-day bladder diary.[13] Diaries were abstracted by a blinded study coordinator. For every void and episode of urine loss, participants recorded the presence and severity of urgency using the Indevus Urgency Severity Scale (IUSS), a 1–3 rating scale.[14]

Secondary patient-reported measures included changes in symptom questionnaires, condition-specific quality of life, satisfaction with treatment, and safety of the treatments. The ICIQ-UI was used to measure UI severity (range 0–21).[15,16] The ICIQ-OAB questionnaire was used to assess the severity of OAB symptoms, range 0–16 (4 items).[17] A validated measure was used to assess patient satisfaction and perception of improvement with treatment using a 5-point Likert scale (very dissatisfied to very satisfied and much better to much worse).[18]

Side effects and unanticipated events were collected by the participant's self-report at phone visits and at the 6-week and 12-week in-person visits. Blood samples were analyzed to monitor changes in calcium, albumin, and vitamin D levels at 6 weeks and 12 weeks. Pill counts were used to assess adherence to drug therapy.

Other secondary outcomes related to possible mechanisms of improvement included pelvic floor muscle strength (Brink's score) before/after treatment,[19] anal sphincter strength (DRESS score),[20] and the Timed Up and Go Test, a validated measure of mobility.[21]

Power Calculations

The primary aim was to estimate change in UUI episodes over time with vitamin D supplementation compared to placebo in order to design and power a larger, more definitive efficacy trial. We calculated that 200 participants (100 in each group) were required to achieve 80% power, assuming a two-tailed Type I error rate of 0.05, a common standard deviation (SD) of change of 3.0 episodes per week, and a clinically relevant 1.2 episodes per week greater decrease in the vitamin D arm compared to placebo. With this pilot study, we examined whether our a priori clinically relevant effect size of a reduction of at least 1.2 episodes/week (40% decrease from the inclusion criterion of ≥3 episodes/week) was in the 95% confidence interval for the difference between the two treatment means. We conducted a pre-planned interim analysis and the conditional power was less than 60%; thus, the treatment differences were less than 1.2 episodes/week.

Statistical Analyses

We evaluated a completer analysis and an intention to treat analysis using last observation carried forward for the primary outcome. The percentage change from baseline to 12 weeks in UUI episodes and secondary outcomes were compared between the two groups using a paired t test and the Wilcoxon signed rank test when appropriate, along with 95% confidence intervals (CI). Multivariable models were constructed in order to estimate 95% CI for treatment effects after controlling for demographics and baseline characteristics. Point estimates and conditional power were performed using SAS version 9.0 statistical software (SAS Institute).

RESULTS

Supplemental Figure 1 summarizes participant recruitment, enrollment, randomization, and completion. Serum 25(OH)D level >30 ng/mL was the primary reason for exclusion (70% of the participants enrolled). No differences in drop-out rates were noted from the vitamin D arm compared to placebo (11% vs 7%, p=1.0) or among women who did not complete their bladder diary (18% vs 11%, p=0.7).

Most baseline demographics did not differ across treatment arms (Table 1). Women in the active vitamin D arm, compared to the placebo arm, reported less current tobacco usage, higher rates of prior hysterectomy, and less obesity, despite no difference in mean BMI. UUI episodes were lower at baseline in the Vitamin D arm compared to the placebo arm (2.6 ±2.1 vs 3.7 ±2.6, p=0.05). Serum 25(OH)D levels were higher in the vitamin D arm compared to the placebo arm (21.2 ng/mL vs 18.2 ng/mL, p=0.05) at baseline with increases only seen in the vitamin D arm at 6-weeks and 12-weeks (p <0.001, Supplemental Figure 2). Adherence to therapy was approximately 97.7% across all arms (96.2% for vitamin D compared to 99.3% for placebo, p=0.75).

When evaluating the overall percent change in UUI episodes (Figure 1 and Supplemental Table 2), we found larger reductions for UUI episodes in the vitamin D arm compared to the placebo arm for the women completing the study and the intention to treat analysis. In further exploratory analysis among high-risk sub-groups (Figure 1), Black women (n=33) had greater reductions in UUI episodes with vitamin D compared to placebo. In obese women (n=32), reduction in UUI episodes did not differ by arm.

Seven-day bladder diary (Table 2) data were used to calculate within-arm and between-arm 12-week changes in daytime frequency, nocturia episodes, daytime urgency, and nighttime urgency. Women in both arms experienced improvements in daytime urgency, but without between-arm differences. We did not find significant differences between arms in daytime voiding frequency or nocturia episodes. However, women in the placebo arm had improvement in nighttime urgency scores.

We found no between-arm differences for the 12-week change in UI and OAB severity questionnaires, nor were there differences in perceived improvement of satisfaction with treatment (Table 2). We also found no between-arm differences in changes in pelvic floor muscle strength, anal sphincter muscle strength, or Timed Up and Go testing.

With regard to adverse events (Supplemental Table 3), one hospitalization occurred for a women on vitamin D who had palpitations. Two participants in the vitamin D arm experienced transient asymptomatic hypercalcemia at 6-weeks (p=0.04 between groups) that resolved at 12-weeks (p=0.68) after holding vitamin D_3. Gastrointestinal symptoms were higher among women taking vitamin D compared to placebo.

DISCUSSION

We designed and conducted a pilot clinical trial to address the impact of optimal vitamin D levels for improving UUI. Although some groups advocate vitamin D levels of 30 ng/mL or

greater, the Institute of Medicine defines vitamin D repletion as a level of 20 ng/mL or less.[22] Among post-menopausal women with vitamin D insufficiency and UUI, high-dose cholecalciferol had a smaller than predicted effect compared to placebo which had a larger, unanticipated effect on UUI episodes after 12 weeks. Our pilot study results provide data to support future studies with adequate power for determining the effects of vitamin D for improving UUI with maintained serum 25(OH)D levels at 30 ng/mL or greater, especially among Black women who may have higher risk for vitamin D insufficiency and UUI.

Even if vitamin D alone does not improve UUI in a larger clinical trial, repleting women with vitamin D insufficiency may help improve outcomes related to other UUI treatments. Increasing evidence in humans and rats has shown that vitamin D may be involved in the regulation of detrusor muscle contraction.[2,23] Using vitamin D or vitamin D analogues may decrease detrusor overactivity when used with other anti-muscarinic agents, or other behavioral interventions, especially in women who have vitamin D deficiency.

Recent data also suggest a need to identify women at higher risk of vitamin D insufficiency, such as Black women and obese women. OAB symptoms and UUI disproportionately occur in Black women,[24] and vitamin D deficiency is common as well (pigmentation reduces vitamin D production).[25] To our knowledge, no large studies of vitamin D and bladder symptoms have focused on Black women. Additionally, obesity lowers bioavailability of vitamin D,[25] and obesity is a risk factor for OAB and UUI; yet, no studies have examined how vitamin D supplements may reduce bladder symptoms in obese women. Our results suggest that Black women may have larger reductions in UUI episodes with vitamin D supplementation compared to placebo. However, obese women did not have similar responses to vitamin D supplementation.

Our trial has strengths and limitations. We recruited a high percentage of treatment naïve women (62%) and African American women with UUI (71%). Attrition was low (10%), adherence to study medication was excellent, and the dosing regimen was effective in raising serum 25(OH)D. The 25(OH)D levels were measured by a laboratory that maintains high quality standards and is VitDQAP approved.[11] Finally, we adjusted cholecalciferol doses to maintain 25(OH)D levels greater than 30 ng/mL in the high-dose arm, with sham adjustments in other arms to maintain blinding. Limitations include that individuals participated for only 12-weeks; perhaps longer exposure to high-dose cholecalciferol would yield greater effects on improving UUI episodes. Self-monitoring using the bladder diary could have had some impact to reduce UUI in both groups by increasing attention to urgency episodes. Lastly, we were not able to recruit the sample size needed for sufficient power to detect differences between the groups for this pilot study. Based on the effect size in this pilot study, a total of 548 women with UUI and low 25(OH)D would provide sufficient power to detect differences in a larger study.

Twelve weeks of high-dose cholecalciferol given to postmenopausal women with 25(OH)D levels less than 30 ng/mL had a lower than expected effect size on UUI without clinically meaningful beneficial effects on other bladder symptoms, pelvic floor muscle function, or functional status. In an exploratory subgroup analysis, Black women with UUI and low vitamin D did have at least a 40% improvement in UUI with high-dose cholecalciferol.

Further investigation of vitamin D_3 alone or in combination with other treatments for UUI may be warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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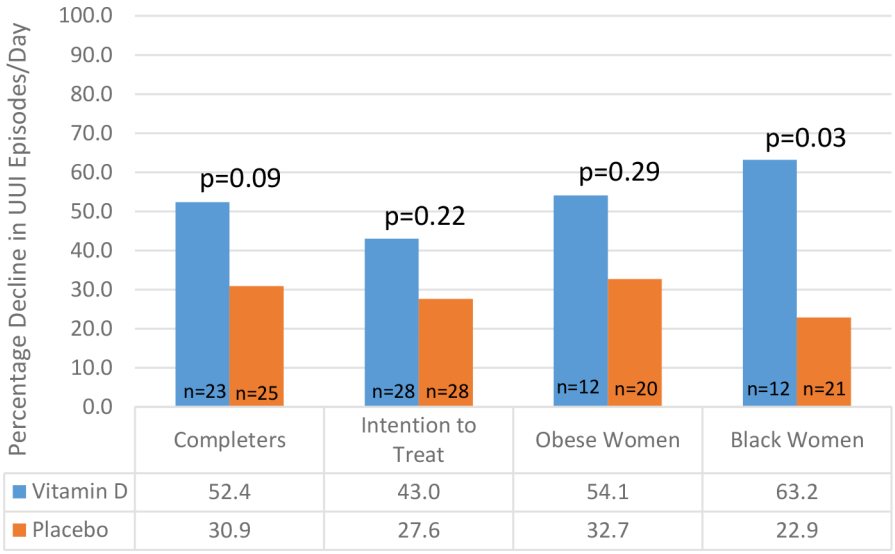

Figure 1:

Comparison of the Percentage Change in Urgency Urinary Incontinency Episodes for Women Randomized to Vitamin D and Placebo for the Completer Analysis, Intention to Treat Analysis, and Higher Risk Subgroups

Table 1.

Characteristics of Participants According to Randomization Group

Data presented as mean ± SD or N (%)	Total Group N=56	Vitamin D3 N=28	Placebo N=28	P value
Age (years) (range)	60.5 ± 8.6 (50–84)	61.4 ± 7.1 (50–84)	59.5 ± 9.2 (50–74)	0.37
Race/Ethnicity				0.08
Non-Hispanic White	16 (29.1%)	12 (42.9%)	5 (17.9%)	
Non-Hispanic Black	39 (70.9%)	16 (57.1%)	23 (82.1%)	
Insurance				
Private	28 (50.0%)	13 (46.4%)	15 (53.6%)	0.79
Medicare/Medicaid	22 (39.3%)	11 (39.3%)	11 (39.3%)	0.99
Self-pay	11 (19.6%)	5 (17.9%)	6 (21.4%)	0.74
BMI (kg/m2)	34.4 ± 8.7	34.9 ± 10.4	33.8 ± 6.6	0.63
Obese (BMI≥30 kg/m2)	36 (64.3%)	15 (53.6%)	21 (80.8%)	0.03
Waist circumference (inches)	40.5 ± 5.6	40.5 ± 5.8	40.5 ± 5.5	0.99
Number of Medications (prescribed)	4.7 ± 3.9	5.2 ± 4.1	4.2 ± 3.6	0.34
Use of Diuretics	15 (26.8%)	5 (17.9%)	10 (35.7%)	0.23
Current tobacco usage	6 (16.1%)	1 (3.6%)	8 (28.6%)	0.02
Prior treatment of UI	21 (37.5%)	12 (42.9%)	9 (32.1%)	0.58
Type of prior UI treatment				
Medications	19 (33.9%)	11 (39.3%)	8 (28.6%)	
Pelvic floor muscle exercises	12 (21.4%)	7 (25.0%)	5 (19.9%)	
Surgery	0	0	0	
Functional Co-morbidity Index (score)	3.3 ± 2.0	3.4 ± 2.2	3.1 ± 1.9	0.60
Diabetes	11 (19.6%)	3 (10.7%)	8 (28.6%)	0.18
Hypertension	30 (58.6%)	11 (39.9%)	19 (67.9%)	0.06
Congestive Heart Failure	2 (3.6%)	0	2 (7.1%)	0.50
Hysterectomy	32 (57.1%)	20 (74.1%)	12 (44.4%)	0.05
Parity	2.8 ± 1.6	2.6 ± 1.4	3.0 ± 1.8	0.29
Baseline Total UUI Episodes/ day	3.2 ± 1.6	2.6 ± 2.1	3.7 ± 2.6	0.05

Table 2.

Secondary Outcomes from Questionnaire and Examination Data at Baseline and After Treatment with Vitamin D3 and Placebo

N=56	Vitamin D3 Mean (SD)		P value*	Placebo Mean (SD)		P value*	Overall p value**
7-day Bladder Diary Outcomes	Baseline	Post-treatment		Baseline	Post-treatment		
Total UUI episodes/day	2.60 (2.13) n=28	1.57 (2.75) n=23	0.04	3.68 (2.58) n=28	2.33 (2.73) n=25	0.006	0.62
Average Voids/day	7.68 (2.58) n=28	7.20 (2.64) n=22	0.09	9.03 (8.90) n=28	8.90 (4.19) n=25	0.565	0.40
Average Voids/night	1.50 (1.24) n=28	1.26 (1.22) n=22	0.37	2.09 (1.74) n=27	1.51 (1.79) n=25	0.036	0.40
Average Urge Rating/day	1.95 (0.85) n=28	1.57 (0.61) n=20	0.04	1.85 (0.59) n=28	1.48 (0.62) n=25	0.016	0.91
Average Urge Rating/night	1.29 (0.54) n=26	1.26 (0.64) n=17	0.79	1.59 (0.72) n=26	0.88 (0.64) n=23	<0.001	0.010
Symptom Severity Questionnaires	Baseline N=28	Post-treatment N=28		Baseline N=28	Post-treatment N=28		
ICIQ-UI	11.6 (5.4)	6.6 (4.5)	0.006	12.5 (4.9)	6.9 (5.4)	0.002	0.81
ICIQ-OAB	9.6 (2.9)	7.3 (2.8)	0.02	10.1 (3.0)	7.1 (3.1)	0.002	0.47
Improvement and Satisfaction†	6-weeks	12-weeks		6-weeks	12-weeks		
Improvement (better, much better)	50.0% (10/20)	70.0% (14/20)	0.03	40.9% (9/22)	77.2% (17/22)	0.09	0.22
Satisfaction (completely)	75.0% (15/20)	63.6% (14/22)	0.26	68.2% (15/22)	85.0% (17/20)	0.32	0.20
Physical Examination	Baseline	Post-treatment		Baseline	Post-treatment		
PFM Strength - Brinks' Score (range 3–12)	5.9 (1.1) n=28	5.9 (1.3) n=25	0.42	5.5 (1.5) n=28	5.6 (1.3) n=23	0.43	0.17
Anal Strength - DRESS Score (range 1–12)	5.2 (1.2) n=27	5.1 (1.7) n=23	0.58	5.2 (1.6) n=26	5.3 (1.2) n=21	0.38	0.63
Timed Up and Go (seconds)	12.1 (3.2) n=25	12.1 (4.0) n=25	0.52	14.5 (8.8) n=27	16.1 (11.6) n=24	0.71	0.06

Note: Data included in Table from women who completed the study.

*p-value for Within-Group Change;

**p-value for Between-Group Change;

†Improvement and Satisfaction with treatment only applies to treatment response at 6-weeks and 12-weeks.

PFM = pelvic floor muscle