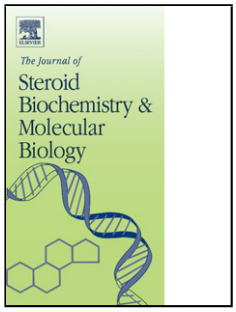

Title: High dose vitamin d may improve lower urinary tract symptoms in postmenopausal women

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PII: S0960-0760(17)30078-X
DOI: http://dx.doi.org/doi:10.1016/j.jsbmb.2017.03.013
Reference: SBMB 4913

To appear in: *Journal of Steroid Biochemistry & Molecular Biology*

Received date: 10-8-2016
Revised date: 14-3-2017
Accepted date: 17-3-2017

Please cite this article as: Johanna Oberg, Margareta Verelst, Rolf Jorde, Kevin Cashman, Guri Grimnes, High dose vitamin d may improve lower urinary tract symptoms in postmenopausal women, Journal of Steroid Biochemistry and Molecular Biologyhttp://dx.doi.org/10.1016/j.jsbmb.2017.03.013

HIGH DOSE VITAMIN D MAY IMPROVE LOWER URINARY TRACT SYMPTOMS IN POSTMENOPAUSAL WOMEN

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Highlights:

- Vitamin D insufficiency is common, and might have extraskeletal consequences.
- Lower urinary tract symptoms (LUTS) are prevalent in postmenopausal women.
- LUTS have been inversely associated with vitamin D intake and status.
- In this RCT, women receiving high dose vitamin D reported improvement in LUTS.
- The results need confirmation in an RCT specifically designed for the purpose.

Abstract

Lower urinary tract symptoms (LUTS) are common in postmenopausal women, and have been reported inversely associated with vitamin D intake and serum 25-hydroxyvitamin D (25(OH)D levels. The aim of this study was to investigate if high dose vitamin D supplementation would affect LUTS in comparison to standard dose. In a randomized controlled study including 297 postmenopausal women with low bone mineral density, the participants were allocated to receive capsules of 20 000 IU of vitamin D_3 twice a week (high dose group) or similar looking placebo (standard dose group). In addition, all the participants received 1 g of calcium and 800 IU of vitamin D daily. A validated questionnaire regarding LUTS was filled in at baseline and after 12 months. At baseline, 76 women in the high dose group and 82 in the standard dose group reported any LUTS. Levels of serum 25(OH)D increased significantly more in the high dose group (from 64.7 to 164.1 nmol/l compared to from 64.1 to 81.8 nmol/l, $p<0.01$). No differences between the groups were seen regarding change in LUTS except for a statistically significant reduction in the reported severity of urine incontinence in the high dose group as compared to the standard dose group after one year ($p<0.05$). The results need confirmation in a study specifically designed for this purpose.

Keywords: Lower urinary tract symptoms; ; ; , vitamin D, RCT, urinary tract infection

1. Introduction

Lower urinary tract symptoms (LUTS) refer to symptoms related to urinary storage and voiding, and include urinary incontinence, urgency and nocturia [1]. LUTS are common among peri- and postmenopausal women, where urinary incontinence affect as many as 30-50% [2, 3]. These symptoms have considerable costs both for the individual and the society [4], and are also associated with reduced quality of life, anxiety and depression [4, 5].

Vitamin D is produced in the skin when exposed to UVB-radiation. In addition, it may be obtained through fatty fish, marine liver oils, fortified food and supplements in the diet. In the body, it is rapidly converted in the liver to the form 25-hydroxyvitamin D (25(OH)D), which currently is the preferred measure of the body's vitamin D status. To become active, a further hydroxylation takes place in the kidney, tightly regulated by - among other factors – parathyroid hormone. In addition, there is strong evidence for extrarenal activation in various tissues regulated by local factors as well as substrate availability [6].

In addition to its role in regulating calcium and phosphorous metabolism and thereby skeletal integrity, vitamin D seems to be involved in a number of other processes like cell growth and differentiation and immune modulation [6]. The vitamin D receptor is distributed in many types of cells and organs in the body, including bladder [7] and muscle [8]. Muscular hypotonia was described as a feature of rickets, the hallmark disease of vitamin D deficiency, already in 1650 [9] and an association between serum 25(OH)D levels and muscle strength has later been described in several studies [10]. Also, a recent meta-analysis found a weak positive benefit of vitamin D intervention on global muscle strength, with a stronger benefit in adults with baseline serum 25(OH)D levels < 30 nmol/l, as well as in those above 65 years of age [11].

Vitamin D could therefore possibly affect LUTS through pelvic floor strength and/or detrusor muscle activity, as also suggested by others [7, 12]. This is supported by epidemiological data where an inverse association between vitamin D intake and the one-year incidence of overactive bladder was reported in a longitudinal study in 6371 women [13]. In another study in 1881 women, women with pelvic floor disorders had lower levels of serum 25(OH)D, and 25(OH)D levels below 75 nmol/l

was associated with increased risk of urinary incontinence in women aged 50 years and older [14]. Also in 1388 men, vitamin D deficiency was associated with urinary incontinence and having at least one LUTS [15]. However, we are not aware of any randomized controlled trial using vitamin D for LUTS in human.

While planning a vitamin D intervention study in postmenopausal women with changes in bone mineral density (BMD) as the primary outcome, we therefore included a validated questionnaire regarding LUTS to have the opportunity to study changes in self-reported LUTS during 1 year of treatment with two different doses of vitamin D.

2. Material and methods

2.1 The study protocol

In 2007-2010, a randomized placebo-controlled trial with vitamin D in postmenopausal women was performed at the Research Unit, University Hospital of North Norway. The study and the results regarding the primary endpoint, changes in BMD, are presented in detail elsewhere [16]. Postmenopausal women aged 50-80 years old with a T-score in total hip or lumbar spine (L2–4) ≤ −2.0 were included. Exclusion criteria were the use of hormone replacement therapy less than 12 month prior to study start, use of steroid treatment, renal stone disease, systolic blood pressure >175 mmHg or diastolic blood pressure >105 mmHg, serum creatinine > 110 µmol/l, primary hyperparathyroidism, ischemic heart disease, cancer, granulomatous disease and diabetes [16].

After inclusion, which took part year-round, all participants received a supplement of 500 mg of calcium and 400 IU of vitamin D_3 to be taken twice daily (Calcigran Forte®, Nycomed, Norway). In addition, the participants were randomized to take either one capsule of vitamin D_3 containing 20,000 IU (Dekristol, Mibe, Brehna, Germany) or a similar-looking placebo capsule (Hasco-Lek, Wroclaw, Poland) twice a week for 12 months. This constituted an average daily dosage of 6500 IU in the high dose group and 800 IU in the standard dose group. Adherence to study medication was assessed by pill counting when returning pill boxes at each 3 months visit during the study where blood samples were taken and adverse events recorded.

2.2 Measurements

2.2.1 Physical measurements

Height and weight were measured in kilograms and meters with participants in light clothing without shoes. BMI was calculated by dividing weight by height^2.

2.2.2 Laboratory measurements

Serum from baseline, every three month control and final 12 months exam were frozen and stored at

−70°C. Serum 25(OH)D was initially analyzed in batch using a liquid chromatography double mass spectrometry (LC-MS/MS) method at the Hormone Laboratory at Haukeland University Hospital [16, 17]. However, in order to standardize our results and make them comparable across different studies and countries, we later re-analyzed our stored samples from baseline and 12 months using the LC-MS/MS method at the *Cork Centre for Vitamin D and Nutrition Research,* which is certified by the Centers for Disease Control and Prevention's Vitamin D Standardization-Certification Program (VDSCP) [18]. In addition to being a participant in VDSCP, the laboratory is monitored on an on-going basis by participation in the Vitamin D External Quality Assessment Scheme (DEQAS) (Charing Cross Hospital, London, UK). These standardized 25(OH)D results will be used in the present paper.

2.2.3 Questionnaires

Medical history, medication and smoking status at baseline were assessed by a clinical interview performed by one medical doctor. In addition, the participants filled in questionnaires both at baseline and the 12 months examination.

Physical activity was measured by having participants report the type (light, moderate or vigorous), frequency and duration of activity per week. Units of metabolic equivalents (MET) were calculated according to International Physical Activity Questionnaire (IPAQ) guidelines using the short 7 days questionnaire. The participants were thereafter categorized into groups of inactive, minimally active or health enhancing active [19].

A questionnaire regarding LUTS from the EPINCONT study was used [20]. In addition, we included questions regarding nocturia (number of times up during night time for voiding) and number of urinary tract infections during the preceding year.

Participants answering "yes" to the question "Do you have involuntary loss of urine?" were defined as having urinary incontinence. Participants answering "no" to this same question, but who answered confirmatively on one of the questions regarding incontinence type, frequency and

amount later in the survey were also included in the urinary incontinence group.

Stress incontinence was defined by answering yes to the question “Do you have involuntary loss of urine in connection with coughing, sneezing, laughing, lifting heavy items?” Participants answering, “yes” to the question “Do you have involuntary loss of urine in connection with sudden and strong urge to void?” were defined as urge incontinent, while those answering “yes” to both questions, were defined as mixed incontinent. Participants answering “yes” to having involuntary leakage of urine, but who answered “no” to the questions on urge and stress incontinence were categorized as not classified. Urgency was defined as answering “monthly, many times per week or daily” to the question “Do you experience sudden and/or strong desire to void which is difficult to suppress?”

Having any LUTS was defined as having any urinary incontinence and/or responding “yes” to either of the questions of having urgency, UTI or nocturia as defined by voiding more than once per night.

A severity index for incontinence was calculated by multiplying the frequency of leakage, (1= less than once a month, 2= Once or more per month, 3 = once or more per week, 4 = every day/ and or night) with the amount of leakage recalculated into two groups (drops or little= 1, more = 2) [21]. This created a three level index; slight incontinent (1-2 points), moderate incontinent (3-4 points) and severe incontinent (6-8 points). This method has been validated against the pad-weighing test where slight incontinent is equivalent to a urinary leakage of 6 g/24hs, moderate to 17 g/24hs and severe to 56 g/24hs [22].

The perceived impact of the incontinence was assessed from the question “how do you experience your leakage problem?”. Those answering “no problem” and “a small nuisance” was categorized as having a “minor problem”, while those answering “some bother”, “much bothered” and “a major problem” was categorized as having a “larger problem”. Significant urine incontinence was defined as having moderate or severe incontinence and at the same time experiencing a larger

problem [20].

2.3 Power and statistics

Power calculations were based on the primary endpoint [16], and no formal power calculation for the change in LUTS has been performed.

Independent t-tests for continuous and chi-square tests for categorical variables were used when comparing the two treatment groups at baseline. There were some deviations from the assumptions of the t-tests, but the result did not change by running the non-parametric Mann-Whitney U test.

To assess change in the different LUTS during the study, the participants changing from having the symptom at baseline to not having it at the final exam, or who reported a decrease in severity or frequency of a symptom during the study, were categorized as “improved”. Those reporting the presence of a symptom at the final exam without having the same symptom at the baseline examination, or an increase in severity or frequency of the symptom during the study, were categorized as “worsened”. Chi square tests were used to compare these changes between the treatment groups. If there were expected cell counts of less than 5 Fisher´s exact test was used. Changes in serum 25(OH)D between the treatment groups were compared using independent t-tests. $P < 0.05$ was regarded statistically significant.

2.4 Ethics

All the participants signed an informed consent before inclusion. The Regional Committee for Medical Research Ethics, the Norwegian Data Inspectorate, and the Norwegian Medicines Agency approved the study, which was registered at ClinicalTrials.gov (NCT00491920).

3. Results

In total 297 participants were included in the study, and 148 in each group filled in the LUTS questionnaire at baseline. During the study, 14 and 8 were lost to follow-up in each group, by reasons elaborated in the flow chart (Fig 1), and for one participant there was no information available regarding LUTS from the final exam. We present data only for the 134 and 139 participants in the high dose and standard dose group with information about LUTS at both measurement points.

Table 1 shows baseline characteristics of the participants. The distribution of LUTS is shown in Table 2. None of the variables were differently distributed between the two groups, and 76 in the high dose vitamin D group and 82 in the standard dose vitamin D group reported symptoms of one or more LUTS. After 12 months of treatment, severity of LUTS symptoms - and the proportion defined as having significant urinary incontinence - improved significantly more in the high dose group (Table 3), while there were no differences regarding the other LUTS variables. Serum 25(OH)D levels increased significantly more in the high dose group (delta value 99.3±31.6 nmol/l in the high dose group and 17.6±17.0 nmol/l in the standard dose group, $p<0.01$).

Adherence was 97% for the study medication (capsules of vitamin D_3 or placebo), and 92% for Calcigran Forte, and did not differ between the treatment groups. The numbers and types of side effects did not differ between the groups, as previously reported in detail elsewhere [16].

4. Discussion

Postmenopausal women treated for one year with high dose vitamin D reported improvement in severity of LUTS as compared to those treated with standard dose vitamin D.

This randomized placebo-controlled study has several strengths. There were few lost to follow-up, and adherence to the study medication was excellent. This was also confirmed by a substantial increase in measured serum 25(OH)D in both groups, as measured by a VDSCP-certified method, and significantly more in the high dose group. A validated questionnaire was used to assess the LUTS symptoms.

There are also several limitations. Most important, the study was not designed for the present purpose, and LUTS was a secondary outcome. Thus, inclusion was based on bone mineral density and not of the presence of LUTS. Although LUTS was quite prevalent in this population, there was a loss of power since more than 40 % of the population reported no symptoms at any of the measurement time points. Also, the majority with symptoms reported minor complaints.

Vitamin D insufficiency or deficiency were not part of the inclusion criteria. Serum 25(OH)D was measured after study completion, and revealed that 75% of the participants were vitamin D sufficient already at baseline, as defined by > 50 nmol/l. If there was a causal relation between vitamin D and LUTS, it is unexpected that an effect should be obvious at such high baseline levels.

We did not adjust for multiple comparisons, and the statistical significant reduction in urinary incontinence severity may be by chance. We have not identified other clinical trials using vitamin D_3, although several studies have used vitamin D analogues. In a small study in rats with bladder outlet obstruction, the vitamin D_3 analogue BXL628 did not prevent bladder hypertrophy, but it appeared to reduce the negative functional changes of the detrusor smooth muscle, thus preserving the emptying of the bladder [12]. Also, Elocalcitol, a synthetic vitamin D analogue, was used in a 4-week intervention study including 308 women with overactive bladder. There was no change in urodynamic measures, but those receiving Elocalcitol reported reduction in number of incontinence episodes and improvement in the Patient Perception of Bladder Condition Questionnaire as compared to those receiving placebo [23]. The same vitamin D analogue was used in animal models where it reduced signs of detrusor overactivity in rats and exerted strong suppressive effect on urinary bladder sensory signalling during filling in mice [24].

We did not find any difference between the groups in reported UTIs during the study period. Several observational studies have reported lower serum 25(OH)D levels in persons with UTIs, both in children [25], adults [26], premenopausal women [27], and after renal transplantation [28]. Recently, significantly less UTI infections were reported in the active group in a 5 year intervention

study with vitamin D in persons with prediabetes [29]. In our cohort, there was relatively few participants reporting urinary tract infections last year at baseline, and even fewer reporting this during the study. We had therefore neither the power nor the optimal population for assessing a possible effect of vitamin D on urinary tract infections.

As LUTS affect many women during the life course and is associated with reduced quality of life while leading to considerable discomfort and costs, finding ways of preventing this is of considerable importance. Vitamin D insufficiency is common worldwide [6], and is easy and cheap to prevent and treat. With a number of limitations, our results are suggestive of an possible role of vitamin D in improving LUTS, but to confirm this, an intervention study in a properly powered target population of women with both LUTS and vitamin D insufficiency should be performed, and the optimal dose or target serum 25(OH)D level must be settled.

Acknowledgements

The study was funded by the Norwegians Women Public Health Association in Troms. The serum 25(OH)D re-analysis was supported by funding received by some of the authors from the European Commission under its Seventh Framework Programme (ODIN; grant agreement no. 613977). We are grateful for the generous supply of Calcigran Forte from Nycomed Norway.

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Legends to figure

Fig. 1 Flow chart

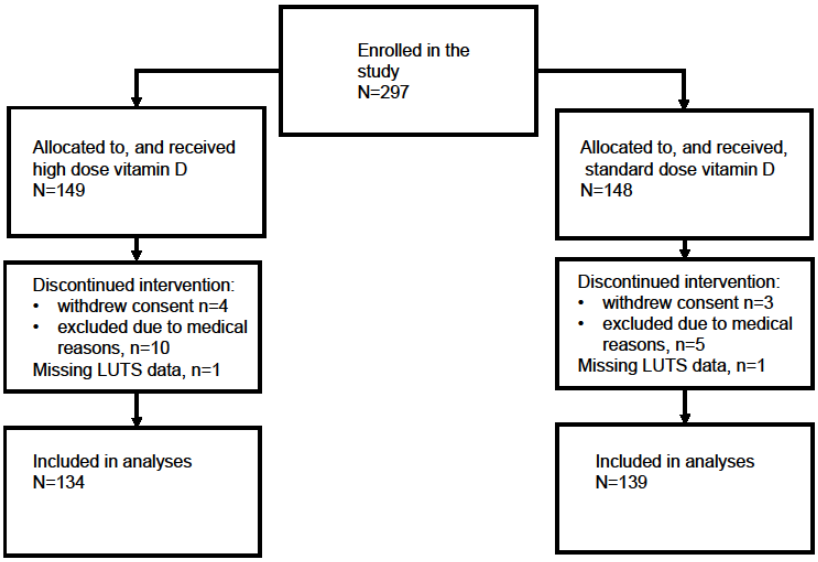

Table 1. Baseline characteristics of the participants

Age (y)	62.8±7.5	63.4±6.9
Serum 25(OH)D (nmol/l)	64.4±21.1	64.2±20.1
Current smoking (%)	22	24
BMI (kg(cm^2)	24.9±3.4	24.6±3.3
IPAQ category (%)[1]		
Inactive	22	25
Minimally active	42	41
HEPA	36	34
Prior hysterectomy, %	12	14

	High dose vitamin D group n=134	Standard dose vitamin D group n=139

BMI; body mass index, IPAQ; International Physical Activity Questionnaire, HEPA; health enhancing physically active

[1]Data missing for 17 participants

Table 2. Baseline characteristics of LUTS

	High dose vitamin D group n=134	Standard dose vitamin D group n=139
Any LUTS	76	82
Any UI	60	63
Type of UI		
stress	23	26
urge	9	16
mixed UI	19	15
not classified	9	6
Severity of UI		
slight	29	32
moderate	7	14
severe	16	10
Self-perceived impact of UI		
no problem	17	16
a small nuisance	21	31
some bother	15	8
much bothered	3	1
a great problem	2	3
Significant urine incontinence	15	7
Urgency		
monthly	35	37
weekly	19	13
daily	10	9

UTI last year	21	19
Nocturia>1	14	21

LUTS; lower urinary tract symptoms, UI; urinary inconctinence, UTI; urinary tract infection

All numbers are n.

Table 3. Changes in LUTS after 12 months with high dose or standard dose vitamin D

	High dose vitamin D group 134	Standard dose vitamin D group 139	p-value
Any LUTS			
improved	21	19	NS
worsened	17	12	
Any urinary incontinence			
improved	20	12	NS
worsened	18	10	
Severity index			<0.05
improved	7	2	
worsened	3	10	
Significant UI			
improved	6	3	<0.05
worsened	0	5	
Urgency			
improved	25	18	NS
worsened	11	13	
UTI			
improved	4	6	NS
worsened	8	11	
Nocturia			NS
improved	4	3	
worsened	7	7	

LUTS; lower urinary tract symptoms, UTI; urinary tract infection, UI; urinary incontinence, NS; not significant

All numbers except for p-values are n.