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Original Research

The Relationship between Vitamin D Level and Lower Urinary Tract Symptoms in Women

Sibel Ocak Serin,[1] Ozlem Pehlivan,[1] Aysun Isiklar,[2] Ahmet Tahra,[3] Sema Ucak Basat[1]

[1]Department of Internal Medicine, University of Health Sciences Turkey, Umraniye Training and Research Hospital, Istanbul, Turkey
[2]Department of Internal Medicine, Acibadem Hospitals Group, Istanbul, Turkey
[3]Department of Urology, University of Health Sciences Turkey, Umraniye Training and Research Hospital, Istanbul, Turkey

Abstract

Objectives: In the literature, the effects of vitamin D on lower urinary tract symptoms (LUTS) have been investigated. Conflicting results have been reported in these studies conducted. LUTS is more common in women. In this study, we aimed to evaluate the relationship between vitamin D and LUTS in female patients using the uroflowmetric method.

Methods: This retrospective cohort study included 186 female patients who were admitted with LUTS. Demographic characteristics, medical history, calcium (Ca) and vitamin D, including laboratory studies and uroflowmetry results, as maximum urine flow rate (Qmax), average urine flow rate (Qav) and voided volume (V) were recorded. Patients were divided into two groups according to age (18-50 and ≥51) and vitamin D levels (<20 and ≥20). Laboratory parameters and uroflowmetry results were compared between groups.

Results: Mean age was 56.85±12.95 years. Mean vitamin D level was 21.19±13.93 ng/mL (2.5-83.5). Mean Qmax value was 35.41±12.63, whereas the mean Qav was 19.13±9.89, and the mean V was 446.60±165.08 mL. Vitamin D levels differed according to age groups (p=0.044). No significant difference was observed between groups according to Qmax, Qav and V values (p>0.05). No significant correlation was detected between vitamin D level and Qmax, Qav and V values. However, a negative correlation was detected between serum Ca level and V values (p=0.042) in the low vitamin D group.

Conclusion: There was no direct relationship between vitamin D levels and LUTS in respect to uroflowmetry. However, we determined that Ca levels affect the uroflowmetry parameter in patients with low vitamin D levels. There is a need for further studies emphasizing serum Ca levels in addition to vitamin D levels in patients with LUTS.

Keywords: Calcium levels; uroflowmetry; lower urinary tract symptoms; vitamin D; women.

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The lower urinary tract symptoms (LUTS) is a common problem in women of all ages, which becomes increasingly severe by advancing age and negatively impacts the quality of life.[1, 2] More than 200 million people encounter this problem worldwide, and it affects women more commonly than men, with a prevalence ranging from 15% to 52%.[3] The LUTS manifests with several symptoms, including storage (frequency, urge incontinence, hyperactive bladder), voiding (intermittent urination, irregular stream, dripping after urination, straining to urinate) and post-

Address for correspondence: Sibel Ocak Serin, MD. Saglik Bilimleri Universitesi Umraniye Egitim ve Arastirma Hastanesi Ic Hastaliklari Klinigi, Istanbul, Turkey
Phone: +90 216 632 18 18 **E-mail:** rdsibelocak@gmail.com

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voiding symptoms (feeling of incomplete bladder emptying, terminal dripping). Urodynamics are used to identify LUTS etiology and for monitoring before and after treatment. Uroflowmetry is the most important urodynamics and comprises a major component in the evaluation of patients. It has a negative predictive value of 97.3% for the exclusion of abnormal voiding dysfunction.[4-6]

In recent years, studies have been conducted, which reported an increased incidence of pelvic floor dysfunction (PFD). These studies demonstrated that LUTS, such as urinary incontinence or frequency, are more common in patients with vitamin D deficiency. In a recent prospective randomized study, the findings showed that high-dose vitamin D supplementation improved LUTS. The majority of studies on LUTS generally use questionnaires, and there are limited studies using uroflowmetry data. In a study using urodynamic assessment by uroflowmetry, it was shown that men 50 years with LUTS had lower vitamin D levels than those without LUTS.[7-9]

In this study, we aimed to evaluate the relationship between LUTS and vitamin D with uroflowmetry parameters in female patients.

Methods

In this cohort, we evaluated female patients who admitted to urology outpatient clinic with LUTS such as urgency, nocturia, pollakiuria or urge incontinence between January 1, 2017 and December 31, 2017. The patients with documented UTI, diabetic patients with disease duration >5 years or neurogenic bladder dysfunction secondary to another neurological disorder, pregnant women, those had delivery within prior six months, patients with stone disease of bladder or ureteral stone, and those with malignancy, patients who had surgery or radiotherapy on the pelvic area, urinary system obstruction or acute renal failure were excluded from this study. The data regarding demographic characteristics involving Ca, vitamin D, serum creatinine and Qmax, Qav and V were recorded from uroflowmetry results. If there were more than one vitamin D and Ca measurements within the prior year, the average value was used for analysis. Patients were divided into two groups according to age and vitamin D levels. 20 ng/mL was used as cut-off value for vitamin D.[10, 11] Laboratory parameters and uroflowmetry results were compared between groups. The authors confirm the availability of, and access to, all original data reported in this study.

Statistical Analysis

The statistical analyses were performed using NCSS 2007 (Number Cruncher Statistical System; Kaysville, Utah, USA). Student's t-test was used for group comparisons of normally distributed two groups. Descriptive statistics like mean, standard deviation, median, frequency, ratio, min-max were used. There were variables were with normal distribution while the Mann-Whitney U test was used for variables with skewed distribution. One-way ANOVA test was used to compare data with normal distribution, while the Kruskal-Wallis test was used to compare data with skewed distribution among three groups. Binary comparisons of data with normal distribution were achieved by Bonferroni's test. Pearson chi-square and Fisher-Freeman-Halton tests were used to compare qualitative data. Spearman's correlation coefficient was used to assess relationships among variables. A p-value <0.05 was considered statistically significant.

Results

This study included 186 patients who presented to the urology outpatient clinic. Mean age was 56.85±12.95 years. 24.2% of the patients were in the 18-50 age group and 75.8% were in the ≥51 group. The mean vitamin D level was 21.19±13.93 ng/mL. The findings showed that the vitamin D level was <20 ng/mL in 104 patients (55.9%), whereas ≥20 ng/mL in 82 patients (44.1%). There was no difference in vitamin D levels according to the age of all patients (p=0.08), and vitamin D was lower in the 18-50 age group and 18-50 age group than the age group ≥51 (p=0.044). Ca levels were significantly lower in patients with low vitamin D when compared to those with normal vitamin D levels (p=0.008). The patients with hypertension were more likely to have normal vitamin D levels (p=0.01; p<0.05). In addition, significant differences were detected in vitamin D levels according to hyperlipidemia presence (p=0.021; p<0.05). The patients with hyperlipidemia were also more likely to have normal vitamin D levels (Table 1).

A positive correlation was detected between blood Ca level and vitamin D levels (r=0.194; p=0.008; p<0.001) (Table 2). There was no statistically significant relationship between age, creatinine, Qmax, Qav and V and vitamin D level (p> 0.05) (Table 2). However, it was found that there was a weak but significant negative correlation between Ca and V levels according to vitamin D levels (r: -0.199; p=0.42; p<0.05) (Table 3).

Discussion

Currently, LUTS is a critical issue due to its prevalence. In our study, the primary aim was to assess the relationship between vitamin D levels and LUTS. The majority of patients were over 50 years of age, which can be counted in the postmenopausal period. Vitamin D was found lower in

Table 1. Assessments according to vitamin D levels

	Vitamin D (ng/ml)			
	Total (n=186)	**<20 (n=104)**	**≥20 (n=82)**	**P**
Age (year)				
Mean±SD	56.85±12.95	55.43±14.16	58.65±11.07	[a]0.084
18-50	45 (24.2)	31 (29.8)	14 (17.1)	[c]0.044*
≥51	141(75.8)	73 (70.2)	68 (82.9)	
Ca (mg/dl)	9.40±0.48	9.32±0.52	9.50±0.40	[a]0.008**
SCr (mg/dl)	0.78±0.24	0.79±0.3	0.77±0.12	[b]0.496
Qmax (ml/sn)	35.41±12.63	34.88±12.87	36.07±12.36	[a]0.525
Qav (ml/sn)	18.60±6.77	18.13±6.62	19.18±6.95	[b]0.417
V (ml)	446.60±165.08	438.96±173.81	456.28±153.81	[b]0.726
HT	115 (61.8)	56 (53.8)	59 (72)	[c]0.012*
DM	92 (49.5)	51 (49)	41 (50)	[c]0.896
CVD	17 (9.1)	9 (8.7)	8 (9.8)	[c]0.796
HL	46 (24.7)	19 (18.3)	27 (32.9)	[c]0.021*
Diuretic	24 (12.9)	13 (12.5)	11 (13.4)	[c]0.853

[a]Student t-test; [b]Mann-Whitney U Test; [c]Pearson Ki-kare Test; [f]Fisher-Freeman-Halton Test; *p<0.05; Ca: Calcium; SCr: Serum creatinine; Qmax: maximum urine flow rate; Qav: average urine flow rate; V: voided volume; HT: Hypertension; DM: Diabetes mellitus; CVD: Serebrovascular desease; HL: Hyperlipidemia.

Table 2. The correlation analysis between uroflowmetry parameters and vitamin D levels

	Vitamin D (ng/ml)	
	r	**p**
Age (year)	0.095	0.198
Ca (mg/dl)	0.194	0.008**
SCr (mg/dl)	0.111	0.133
Qmax	0.094	0.204
Q ort	0.104	0.158
V	0.068	0.355

r: Spearman's Correlation Coefficient**p<0.01; Ca: Calcium; SCr: Serum creatinine; Qmax: maximum urine flow rate; Qav: average urine flow rate; V: voided volume.

women under the age of 50 compared to those over 50. There was no relationship between age, urodynamic results, and vitamin D. However, in cases with a low vitamin D levels, there was an inverse relationship between Ca and V as the Ca level decreased and the amount of urine increased. As a secondary outcome, we found that vitamin D levels were higher in patients with HT or hyperlipidemia. In addition, a negative correlation was detected between serum Ca levels and V measurements.

Pelvic floor is a unique structure where its functions depend on interactions among muscle, nerve, connective tissue and bones. The pelvic floor disorders (PFD) occurs when there is a disruption in these interactions. In many studies, including skeletal muscle cell cultures, experimental animal studies and human research, it was proved that muscle strength and functions are influenced by vitamin, resulting in a reasonable assumption that vitamin D insufficiency or deficiency can be associated with significant consequences for pelvic floor.[12]

In the literature, there are two large epidemiological studies about role of vitamin D levels in PFD in community-dwelling women. In a cohort study conducted by Leices-

Table 3. The correlation analysis between uroflowmetry parameters and calcium according to vitamin D levels

	Vitamin D (ng/ml)					
	<20 (n=104)		**≥ 20 (n=82)**		**Total (n=186)**	
	r	**p**	**r**	**p**	**r**	**p**
Ca - Qmax	-0.069	0.487	0.078	0.487	-0.015	0.834
Ca - Qav	-0.047	0.637	0.103	0.359	0.010	0.892
Ca – V	-0.199	0.042*	0.073	0.513	-0.108	0.142

r: Spearman rank correlation; *p<0.05 Ca: Calcium; Qmax: maximum urine flow rate, Qav: average urine flow rate; V: voided volume.

tershire MRC Incontinence Study Group, it was reported that higher vitamin intake had significant association to reduced risk for overactive bladder (OAB).[13] In the national health and nutrition examination survey (NHANES) cycle (2005-2006), the prevalence of vitamin D insufficiency was reported to be as high as 82% in non-pregnant women aged >20 years by Badalian and Rosenbaum. Moreover, it was reported that urinary incontinence symptoms were lower in the group with sufficient vitamin D levels after adjusted according to demographic factors known to be associated with PFD and vitamin D levels.[14]

TURDEP-II, the most comprehensive study on this subject, examined 9560 adults, and 93% of the samples were vitamin D <20 ng/mL. Likewise, in a meta-analysis, including 40 studies with 111,582 sample sizes published in 2019, vitamin D deficiency was shown as <20 ng/mL.[10, 11] In our study, the mean age was 57 years and the mean vitamin D level was 21 ng/mL. The vitamin D level was >20 ng/mL in 56%, while <20 ng/mL in 44% of patients. There was no difference in vitamin D levels according to the ages of all patients, but vitamin D was lower in the 18-50 age group. In a retrospective study from the USA on 394 women, the mean age was 64.3±12.6 years. Authors defined vitamin D sufficiency as vitamin D level>30 ng/mL and found that there was vitamin D insufficiency in 51% of the study population. In that study, the findings showed that vitamin D level was significantly lower in women with PFD (urgency, frequency, fecal incontinence and pelvic organ prolapse) than healthy controls (29.3±11.5 vs. 35.0±14.1 ng/mL; p<0.001).[15] In a study, including 1881 women aged >20 years, it was found that vitamin D levels were lower than 30 ng/mL in women with urinary incontinence in age group >50 years (17.2% vs. 9.8%). Authors concluded that vitamin D level >30 ng/mL significantly decreased risk for PFD in all women aged >20 years and in the age group ≥50 years.[14]

A Korean study enrolled 6451 women aged >20 years who were participants of the Korea National Health and Nutrition Examination Survey IV. No significant difference was detected in mean vitamin D levels between patients with urinary incontinence and healthy subjects (18.4±6.6 vs. 18.5±7.0 ng/mL; p=0.752). In addition, no significant difference was found in vitamin D level distribution. Authors concluded that low serum vitamin D concentration has no significant or independent association with urinary incontinence in Korean women.[16]

In a study conducted by Aydogmus and Demirdal investigation LUTS frequency in women with vitamin D deficiency and controls, LUTS was assessed using the Bristol Female Lower Urinary Tract Symptoms (BFLUTS) questionnaire. The mean age was 47 years and vitamin D deficiency (<20 ng/ml) was detected in 67.3% of the participants in that study. The Pelvic Floor Muscle Strength was significantly lower in the group with vitamin D deficiency than the controls, but no significant correlation was found between LUTS and vitamin D deficiency.[17]

Vitamin D insufficiency may also affect the detrusor wall and contributes symptoms-related OAB and urge incontinence.[18] In in vivo studies, the findings showed that there was a vitamin D receptor in bladder neck consisting of urothelium and inner longitudinal, middle circular and outer longitudinal smooth muscle layer. Thus, vitamin D receptors may be expressed throughout the bladder wall. As active vitamin D metabolite acts using vitamin D receptor, vitamin D deficiency/insufficiency may lead to disruption Ca homeostasis, resulting in abnormal detrusor contractility. The weak detrusor muscles may gain hyper-contractile features or become irritable. Moreover, serum vitamin D insufficiency may affect urothelium by causing higher inflammatory cytokine activity, resulting in inflammation in the bladder wall. The above-mentioned mechanisms suggest that women with vitamin D insufficiency may have Ca hemostasis abnormality in the detrusor wall and contribute to urinary urgency and urge incontinence symptoms.[19-21] Similarly, it has been proposed that the finding of an association between vitamin D hypovitaminosis and LUTS or urinary tract infection (UTI) may be due to failure in anti-inflammatory and Ca metabolism regulatory effects of vitamin D in a study specifically investigating the association between LUTS, UTI and vitamin D among women.[22]

Uroflowmetry is considered a basic diagnostic tool for evaluating the function of the lower urinary tract. Uroflowmetry is usually performed in out-patient clinics. The main advantage of Uroflowmetry is that it is non-invasive. To have representative results, the voided volume should be between 150 and 400 mL.[4, 5] In our study, there was a positive correlation between vitamin D level and serum Ca. This is anticipated as vitamin D play a role in Ca regulation. Thus, we evaluated this relationship in the context of Ca and uroflowmetry measurements. In cases with low vitamin D level, no significant correlation was detected between Ca and Qmax and Qav. In addition, there was a weak, negative correlation (increasing V by decreasing Ca level) between Ca level and V measurements, which can favor importance of vitamin D measurement together with Ca level in patients with LUTS. In PFD studies, a role different from Ca has been proposed for vitamin D regarding muscle contractility. However, there is a scarcity in the studies addressing the Ca level with or without vitamin D status.[23, 24] Among these, in the study conducted by Dallosso et al.[13] on OAB and nutrients, it was shown that there was a causative relationship between OAB onset and vitamin D, protein and potassium,

but no such relationship was shown regarding Ca. In another study, in a double-blinded, randomized, controlled study involving 122 elder females (mean age: 85.3 years), it was shown that improvement in skeletal muscle functions could be achieved in only patients received 1200 mg Ca plus 800 IU cholecalciferol (vitamin D) when compared to those received Ca alone. Thus, it was proposed that low vitamin D levels favor LUTS development by causing pelvic floor weakness, especially in pelvic floor muscular weakness. Increased intra-abdominal pressure may hamper effective closure of urethra, resulting in LUTS.[24, 25]

In the study of Abdul-razzak et al. on the relationship between OAB and psychological symptoms, serum vitamin D and the amount of Ca taken with daily diet were evaluated together. In the OAB group, vitamin D and dietary Ca intake were significantly lower than the control group. Vitamin D supplementation and increased dairy Ca products intake can be effective in improving OAB symptoms and associated with psychological symptoms and improvement in the quality of life.[26] Since our study was a cross-sectional study, urodynamic evaluation could not be performed after supplementation of Ca and Vitamin D. However, it is important to put an emphasis on the analysis of Ca levels together with vitamin D in cumulative studies in LUTS.

In several studies, it has been suggested that vitamin D insufficiency may be a risk factor for atherosclerotic diseases.[27, 28] As distinct from we found that vitamin D levels were higher in patients with HT or hyperlipidemia. Vitamin D deficiency was common among the adult Turkish population.[10, 11] However, higher vitamin D levels than expected in individuals at risk for vitamin D deficiency, especially in postmenopausal women, maybe due to frequent visits to the hospitals due to chronic diseases, such as hypertension or hyperlipidemia, allowing detection of vitamin D deficiency and vitamin D replacement in these patients. In addition, vitamin D replacement is used more widely in the elderly population as a part of treatment for osteoporosis.[29] We think that these results could be related to vitamin D replacement in these patients.

In the presence of sufficient serum vitamin D levels, the body can compensate for extremely low Ca intake. However, there are several studies reporting inadequate Ca-rich food intake in the normal population. In addition, Ca absorption can be decreased in many conditions, such as menopause, advanced age, thiazide diuretic use and lactose intolerance.[30] Ca also is essential for muscle function and nerve transmission, as well as bone metabolism. As vitamin D replacement alone without Ca supplementation is considered as insufficient in the treatment of osteoporosis,[31] it should be encouraged to assess vitamin D and Ca levels together in pelvic diseases associated with muscular and neural functions.

This study has some limitations. For example, vitamin D levels show seasonal alteration. In addition, since our study is a retrospective study, we do not know the amount of daily calcium intake by diet. We tried to mitigate the effects of these limitations by taking annual averages of vitamin D and Ca levels obtained throughout the year. Another limitation is lacking a control group since uroflowmetry studies are not performed in patients without LUTS.

Conclusion

We found that Ca levels in patients with low vitamin D affect the uroflowmetry parameter. We believe that there is a need for further studies emphasizing serum Ca levels in addition to vitamin D levels in patients with LUTS.

Disclosures

Ethics Committee Approval: This study was approved by the local ethics committee (Approval: 22/06/2018-09.29-54132726-000-14136). This study was conducted in accordance with the Helsinki Declaration and Good Clinical Practices guideline.

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Conflict of Interest: None declared.

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