



# Overactive bladder and associated psychological symptoms: A possible link to vitamin D and calcium

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## Abstract

**Introduction:** Overactive bladder (OAB) is a prevalent syndrome that is associated with multiple urinary tract symptoms and could affect the patient's quality of life and well-being. Vitamin D is shown to be linked to OAB syndrome, which exacerbated by stress conditions. This study evaluated the relationship between vitamin D status, daily calcium intake and OAB, and the associated psychological symptoms.

**Methods:** The study included 55 patients with OAB and 129 healthy controls. Psychological symptoms were assessed using the Hospital Anxiety and Depression Scale (HADS). Serum vitamin D was measured. Patients with OAB with low vitamin D level received orally vitamin D supplementation. Urinary symptoms, psychological symptoms, and quality of life were evaluated before and after vitamin D supplementation plus dairy products.

**Results:** Vitamin D deficiency was more prevalent in cases (80%) vs controls (34.9%). Depression (43.7% vs 20.2%) and anxiety (52.8% vs 10.9%) scores (HADS,  $\geq 8$ ) were also more frequent in cases vs controls, respectively. Some 85.5% of the patients' group had musculoskeletal pain vs 0.0% for the control. Depression was negatively correlated with daily calcium intake and positively with anxiety. Logistic regression analysis revealed that age, vitamin D, and anxiety scores were significant predictors of OAB. Vitamin D supplements with increased calcium intake had significant improvement in urinary symptoms, psychological distress, and quality of life.

**Conclusions:** Vitamin D supplements and improved calcium intake may improve urinary and psychological symptoms and quality of life among patients with OAB syndrome. Assessment for vitamin D status in patients with OAB may be warranted.

## KEYWORDS

anxiety, calcium, overactive bladder, quality of life, vitamin D, vitamin D supplementation

## 1 | INTRODUCTION

Overactive bladder (OAB) is a prevalent cause of lower urinary tract symptoms (LUTS), and is defined as a syndrome of bladder-storage function and characterized by a cluster of symptoms including urinary urgency, frequency, and nocturia with and without urinary incontinence (UI).<sup>1</sup> The prevalence of OAB is increasing with age reaching around 17% in people aged  $\geq 40$  years,<sup>2</sup> and found to be equally distributed between women and men, although women are more likely to present with urgency urinary incontinence.<sup>1</sup> There are multiple urological and nonurological risk factors associated with the development of OAB such as age, obesity, cognitive disorders, metabolic syndrome, neurologic disorders, and benign prostatic hyperplasia.<sup>3</sup> Identification of modifiable risk factors for OAB will potentially hinder the development and progression of OAB symptoms.

Symptoms of OAB may have a detrimental impact on patient's quality of life and could lead to emotional distress, depression, anxiety, and sleep disturbances.<sup>4</sup> Data from the epidemiology of LUTS population-based survey demonstrated the presence of higher percentages of psychological symptoms and health care visits among patients with OAB.<sup>5</sup> OAB patients with anxiety reported more severe OAB/incontinence symptoms.<sup>6</sup>

There is an increasing evidence suggesting that vitamin D deficiency or insufficiency is associated with LUTS. This may be because of the effect of vitamin D on muscle growth and function.<sup>7</sup> For example, a study reported lower levels of vitamin D in elderly males ( $>50$  years) with LUTS ( $n = 70$ ) compared with the controls ( $n = 80$ ).<sup>8</sup> In addition, these symptoms may be attenuated after vitamin D supplementation.<sup>9</sup> However, the effect of vitamin D on the psychological distress and decreased quality of life associated with OAB has not been clarified.

Vitamin D is the single most deficient vitamin and musculoskeletal pain (MSP), and weakness are symptoms found to be accompanied by vitamin D deficiency.<sup>10</sup> Previously, we found that low serum vitamin D level and low daily calcium intake were associated with psychological symptoms among patients with MSP,<sup>11</sup> psychiatric outpatients,<sup>11</sup> and those with noncardiac chest pain.<sup>12</sup> Vitamin D supplementation seems to have a positive effect on all of these comorbidities in outpatients with MSP or psychiatric outpatients.<sup>11,13</sup>

The goals of this study were to (1) characterize the relationship between vitamin D status, daily calcium intake and OAB symptoms and the associated psychological symptoms, (2) identify the prevalence of MSP among patients with OAB, (3) assess the predictors of OAB, (4) evaluate the impact of vitamin D supplementation on symptoms of OAB, psychological symptoms, and quality of life.

## 2 | METHODS

### 2.1 | Participants and setting

This is a case-control study conducted at the University Teaching Hospital (UTH), the main tertiary teaching hospital in the north of Jordan. Cases were recruited from urology outpatient clinics at UTH for the period from February to December 2017. Urologists confirmed patient evaluation and diagnosis clinically and urodynamically. Written informed consents were obtained from all the participants.

The control group included subjects who were apparently healthy, without OAB symptoms, MSP, fatigue or sleep disturbance.<sup>11-13</sup> Subjects excluded were those with chronic diseases affecting vitamin D metabolism including kidney and liver disease and disability diseases, and conditions damaging nerve (such as diabetes mellitus, stroke, and multiple sclerosis), who are not able to complete the questionnaire, and who were on vitamin D supplements for the last 2 months.<sup>12</sup>

All participants were informed about the objectives of the study, agreed to participate, and answered a self-guided questionnaire, which contained sociodemographic health status, disease conditions, localization, and severity of MSP if present. Pain severity was measured using a 0 to 10 Numerical Rating Scale (NRS).<sup>11,13</sup> The patients with OAB answered questions about disease duration and symptoms including daytime urinary frequency, nocturia, enuresis, and UI.<sup>14</sup> Quality of life among patients was assessed using Urgency Severity and Impact Questionnaire (USIQ-QOL) as previously described.<sup>14</sup> Scores were ranged from 0 to 3 and the average score of items was multiplied by 33.333 to generate scores on a scale of 0 to 100. The higher scores (66.67-100) indicating that the quality of life is moderately-greatly and negatively affected by the disease.<sup>14</sup>

Calcium intake was evaluated by self-reporting. Information regarding the participant's frequency (daily, weekly, monthly, and none), and the type of dairy product intake was recorded. Intake of dairy products was determined on daily basis as none, single, two, and three or more dairy servings per day. A dairy serving is defined as: 1 cup of milk or yogurt (300 mg calcium), 2 full tablespoons (2 oz) of labneh (100 mg calcium), and a 1-ounce piece of cheese (162 mg calcium), and cream cheese (20 mg calcium).<sup>11,13</sup>

### 2.2 | Psychological measures

Self-reported symptoms of anxiety and depression were assessed using the Hospital Anxiety and Depression Scale (HADS), which is a simple, reliable, and potentially valid

measure commonly utilized to evaluate anxiety and depression disorders. The study subjects were divided into three groups according to the total HADS score as follows: total score from 0 to 7 indicates normal, 8 to 10 borderline abnormal, and 11 to 21 abnormal or a clinical case with anxiety and depressive symptoms.<sup>15</sup>

### 2.3 | Blood samples

At the baseline visit, nonfasting venous blood samples were drawn for analyses of 25-hydroxyvitamin D (25-OHD) level using a chemiluminescent assay. Vitamin D status was divided into four diagnostic categories according to the serum 1,25(OH)<sub>2</sub>D levels as follows: vitamin D sufficiency ( $\geq 30$  ng/mL), vitamin D insufficiency (20 to  $< 30$  ng/mL), vitamin D deficiency (10 to  $< 20$  ng/mL), and severe vitamin D deficiency ( $< 10$  ng/mL). Assays were performed at the UTH laboratory.

### 2.4 | Participants follow-up

On the basis of the results of vitamin D level, the physician prescribed one vitamin D (50 000 IU) tablet orally per week for 4 weeks for participants with vitamin D insufficiency and one vitamin D (50 000 IU) tablet weekly for 8 weeks for participants with vitamin D deficiency. All participants were informed about the importance of adequate intake of dietary calcium and advised to consume two to three servings of dairy products daily. Participants were re-evaluated for overall improvement in OAB symptoms, MSP severity, and psychological symptoms. Quality of life was also evaluated after treatment using the same questionnaire mentioned earlier (USIQ-QOL). The re-evaluation was conducted within 30 days after the administration of the last dose of vitamin D.

### 2.5 | Statistical analysis

Data are presented as frequencies or mean with standard deviation as appropriate. The  $\chi^2$  test and the Student *t* test (or other nonparametric tests as appropriate) were used to investigate the association between OAB and categorical and continuous variables of interest, respectively. Logistic regression was used to assess the effect of vitamin D deficiency on having OAB adjusting for other potential confounders. One-tailed Spearman's correlation was performed to assess the correlation between psychological symptoms and selected parameters among OAB cases. McNemar's test was used to compare the frequency of urinary symptoms before and after vitamin D supplementation. Paired the Student *t* test was used to compare psychological symptoms and quality of life scores before and after vitamin D supplements. All

statistical significance verifications were conducted at the level of  $P < 0.05$ . Data analysis was performed using the SPSS, version 21.0.

## 3 | RESULTS

### 3.1 | Characteristics of the study population

This study included 55 patients with OAB syndrome of whom 21 (38.2%) were identified as newly diagnosed patients, 34 (61.8%) who were previously diagnosed with primary OAB and unsuccessfully treated by prescribed drugs, and 129 healthy subjects were controls. The two groups aged between 18 and 56 years, 42.6% of cases ( $n = 26$ ) were 40 years or older vs 23.6 ( $n = 29$ ) in controls,  $P = 0.008$ . Females represented 56.4% ( $n = 31$ ) of the patient group and 49.1% ( $n = 27$ ) were married. Fatigue and headache were reported by 76.4% ( $n = 42$ ) and 37.83% ( $n = 17$ ) of the patient group compared with 0.0% and 0.0%, of control, respectively, ( $P < 0.001$ ). Other participants' characteristics are summarized in Table 1.

The majority (85.5%,  $n = 47$ ) of the patient's group had MSP, and 40.0%,  $n = 22$  of them were complaining of chronic MSP (for the duration  $> 3$  years) and 52.7%,  $n = 29$  experienced the pain daily. MSP severity score on NRS was  $5.14 \pm 1.9$ .

### 3.2 | Biochemical parameters among study population

Patients group had significantly lower vitamin D level compared with controls (median [interquartile range] of 12.3 [6.3-18.4] and 27.3 [14.9-35.7], respectively  $P < 0.001$ ). Severe deficiency ( $< 10$  ng/mL) was seen in 40% ( $n = 22$ ) of the patients compared with 16.3% ( $n = 21$ ) of the controls. Only 3.6% ( $n = 2$ ) of patients had a normal level of vitamin D as compared with 41.9% ( $n = 54$ ) of controls (Table 1).

The analysis also revealed that the median of daily calcium intake was significantly lower in patients with OAB than in the control (373.4 mg/day (3.3-1142.7) and 442 mg/day (82.3-2004), respectively;  $P < 0.001$ ).

### 3.3 | Psychological symptoms

Patients with OAB group had markedly higher psychological symptoms than controls (Table 1). HADS-anxiety and HADS-depression were reported by 52.8% and 43.7% of the patients, respectively, while 10.9% of controls had anxiety and 20.2% had depressive symptoms. Also, (32.7%,  $n = 18$ ) of patients with OAB were found to have both anxiety and depression (subscale scores  $\geq 8$ ).

**TABLE 1** Study population characteristics in the total sample and by case-control status

Variables	Cases (n = 55)	Controls (n = 129)	P values*
Age (mean ± SD), y	37.7 ± 17.2	34.2 ± 11.9	0.175
Sex			
Male	24 (43.6)	54 (41.9)	0.823
Female	31 (56.4)	75 (58.1)	
Marital status			
Single	28 (50.9)	62 (48.1)	0.724
Married	27 (49.1)	67 (51.9)	
Body mass index, kg/m <sup>2</sup>			
<18.5	1 (1.8)	6 (4.7)	0.06
18.5-24.9	23 (41.8)	62 (48.1)	
25-29.9	16 (29.1)	46 (35.7)	
≥30	15 (27.3)	15 (11.6)	
Serum vitamin D, ng/mL			
Normal (≥30)	2 (3.6)	54 (41.9)	<0.001
Insufficient (20-29.9)	9 (16.4)	30 (23.3)	
Deficient (10-19.9)	22 (40)	24 (18.6)	
Severe deficiency (<10)	22 (40)	21 (16.3)	
T. calcium intake, mg/d <sup>a</sup>			
≤300	25 (45.5)	38 (29.5)	0.014
300.1-576.7	20 (36.4)	40 (31)	
>576.7	10 (18.2)	51 (39.5)	
HADS-depression			
Normal (0-7)	31 (56.4)	103 (79.8)	0.004
Borderline (8-10)	14 (25.5)	17 (13.2)	
Abnormal (11-21)	10 (18.2)	9 (7)	
HADS-anxiety			
Normal (0-7)	26 (47.3)	115 (89.1)	<0.001
Borderline (8-10)	9 (16.4)	5 (3.9)	
Abnormal (11-21)	20 (36.4)	9 (7)	

Data are presented as n (%) unless otherwise mentioned.

HADS-A, Hospital Anxiety and Depression Scale for anxiety; HADS-D, Hospital Anxiety and Depression score for depression.

\* $P < 0.05$  was considered statistically significant.

<sup>a</sup>T. calcium intake, mg/d=Total daily calcium intake, mg/d (dairy+supplement) stratified as tertile.

### 3.4 | Urinary symptoms

Nocturia was the most frequent symptom among patients with OAB (90.9%,  $n = 50$ ), followed by frequent urination (83.6%,  $n = 46$ ). The majority (85.5%,  $n = 47$ ) of patients had more than eight times urgent urination per day, and 72.8% ( $n = 40$ ) could not wait for less than 5 minutes before urinating.

Most of the 34 patients who previously diagnosed to have OAB were on prescribed drugs. Five patients used drugs for 3 months and the rest of the patients used drugs for more than 3 months. Patients were receiving anticholinergic medications such as Solifenacin (5-10 mg, once daily), which is the first line therapy, Tolterodine (2 mg, twice daily) or Oxybutynin (5 mg, three times daily) to

relieve urinary symptoms. However, these drugs were not effective to resolve OAB symptoms according to the urologist evaluation.

### 3.5 | Spearman's correlation between selected variables

Correlation analysis was conducted to evaluate the relationships between OAB symptoms, psychological symptoms, vitamin D level, total daily calcium intake, MSP severity, age, and body mass index (BMI). Anxiety score was negatively correlated with BMI ( $r^2 = -0.249$ ,  $P = 0.034$ ) and age ( $r^2 = -0.477$ ,  $P < 0.001$ ). Depression score was negatively correlated with daily dietary calcium intake ( $r^2 = -0.26$ ,  $P = 0.028$ ) and positively with anxiety ( $r^2 = 0.440$ ,  $P \leq 0.001$ ). While the number of MSP sites correlated positively and significantly with pain severity ( $r^2 = 0.528$ ,  $P \leq 0.001$ ) and age ( $r^2 = 0.273$ ,  $P = 0.035$ ). None of these symptoms was correlated with vitamin D levels.

### 3.6 | Independent predictors of OAB

Logistic regression showed that age, vitamin D status and anxiety score were significant predictors of OAB syndrome (Table 2). Vitamin D level was the strongest predictor followed by anxiety score. For instance, those with severe vitamin D deficiency (<10 ng/mL) were 31.63 more likely to have OAB symptoms as compared to those with normal vitamin D levels (≥30 ng/mL). Also, the odds of having OAB symptoms in patients with 11 to 21 anxiety score was 13.85 times the odds of symptoms in those without anxiety symptoms.

### 3.7 | Patients follow-up

Patients with OAB involved in the follow-up study were those who were on ineffective drug therapy ( $n = 13$ ), with baseline vitamin D insufficiency ( $n = 2$ ) or vitamin D deficiency ( $n = 11$ ), who sought further consultation and assessment after receiving the results of vitamin D status. In addition, patients completed the first questionnaire and were required to comply with physician recommendation for the number of vitamin D tablets to be taken.

Relative to baseline, most of the measured urinary outcome parameters were significantly improved after vitamin D supplementation and increased daily dietary calcium intake. OAB moderate to severe symptoms of urinary frequency, nocturia, terminal dribbling, and incontinence were significantly less prevalent after receiving vitamin D supplementation and increased daily dietary calcium intake ( $P < 0.05$ ; Table 3).

**TABLE 2** Multivariable logistic regression analysis for predictors of overactive bladder

Variables	Odds ratio	CI (95%) <sup>a</sup>	P values*
Age ≥40	7.27	2.44-21.67	<0.001
Body mass index			
<18.5	Reference		
18.5-24.9	1.38	0.09-19.35	0.739
25-29.9	0.93	0.06-14.60	0.939
≥30	1.52	0.09-24.89	0.769
Serum vitamin D <sup>b</sup>			
Normal	Reference		
Insufficient	13.21	2.05-85.28	0.007
Deficient	30.10	4.83-187.42	<0.001
Severely deficient	31.63	4.86-205.82	<0.001
T. dietary Ca intake, mg/d <sup>c</sup>			
>576.7	Reference		
300.1-576.7	2.32	0.70-7.72	0.167
≤300	2.90	0.88-9.58	0.079
HADS-depression			
Normal 0-7	Reference		
Borderline 8-10	1.80	0.51-6.40	0.361
Abnormal 11-21	0.38	0.09-1.73	0.214
HADS-anxiety			
Normal 0-7	Reference		
Borderline 8-10	16.05	2.89-88.90	0.001
Abnormal 11-21	13.85	3.47-55.28	<0.001

Odds ratio were estimated using multivariable logistic regression. Variables included in the model were those, which were significantly different in the bivariable tests with  $P < 0.2$ . Statistical significance was set at a two-sided  $P < 0.05$ . HADS-anxiety, Hospital Anxiety and Depression Scale subclass score for Anxiety; HADS-depression, Hospital Anxiety and Depression Scale subclass score for Depression, OD, odds ratio.

<sup>a</sup>OR (95% CI)=results represented as odds ratio and 95% confidence intervals.

<sup>b</sup>Vitamin D=Serum vitamin D level, ng/mL, normal  $\geq 30$ , insufficient = 20 to  $<30$ , deficient  $<20$ , severely deficient  $<10$ .

<sup>c</sup>Total calcium intake, mg/d=Total daily calcium intake (dairy+supplement) stratified as tertile.

\* $P < 0.05$  was considered statistically significant.

Supplementation with vitamin D has also significantly improved MSP severity and psychological symptoms in patients with OAB. MSP severity was significantly reduced ( $5.14 \pm 1.9$  vs  $3.09 \pm 2.22$ ;  $P = 0.024$ ). There was a decrease in the mean of HADS-Anxiety (pre:  $11.5 \pm 4.6$  vs post:  $5.8 \pm 3.8$ ;  $P < 0.001$ ) and HADS-Depression (pre:  $9.15 \pm 3.5$  vs post:  $6.15 \pm 2.6$ ;  $P = 0.003$ ) scores, Table 4. Interestingly, vitamin D intake had a positive impact on health-related quality of life (QOL score decreased from  $64.5 \pm 22.1$  to  $20.2 \pm 30.1$ ;  $P < 0.001$ ).

## 4 | DISCUSSION

The current study tested the hypothesis that vitamin D and calcium might be involved in the pathophysiology of OAB and associated symptoms. The most notable finding of the current study is the presence of high prevalence of vitamin D deficiency, and associated symptoms (MSP, fatigue, and psychological symptoms) among Jordanian patients with OAB compared with controls. Interestingly and to the best of our knowledge, this is the first study to find that vitamin D supplementation and increased dairy products intake can be effective in improving OAB symptoms and associated psychological symptoms and improved the quality of life.

Vitamin D is a fat-soluble vitamin that exerts critical roles in muscle function such as in the bladder where its receptors are expressed.<sup>16</sup> Previously, higher total OAB symptom score was reported in patients with low vitamin D.<sup>9</sup> The current study observed high prevalence of vitamin D deficiency (80%) among patients with OAB as compared with controls (34.9%), which supports the previous findings that urinary tract symptoms are common in patients with decreased vitamin D level, and suggests that vitamin D deficiency

**TABLE 3** Effect of vitamin D supplementation plus increasing daily dairy products intake on urinary symptoms

	Moderate to severe symptoms (preVit D)	Moderate to severe symptoms (postVit D)	P values*
Nocturia	61.5% (8)	0% (0)	0.005
Enuresis	15.4% (2)	0% (0)	0.157
Urinary incontinence	38.5% (5)	7.7% (1)	0.045
Increased daytime frequency	76.9% (10)	30.8% (4)	0.014
Terminal dribble	46.2% (6)	7.7% (1)	0.025
Daytime urinary frequency	Patients $\geq 8$ episodes (preVit D) 92.3% (12)	Patients $\geq 8$ episodes (postVit D) 23.1% (3)	0.002

Data are presented as % (n). Percentages reported are out of the total number of patients who completed the follow-up survey (n = 13).

Of the 13 patients: vitamin D insufficiency (n = 2) and vitamin D deficiency (n = 11).

Data were analyzed using the McNemar test. Vit, vitamin.

\* $P < 0.05$  is considered statistically significant.

**TABLE 4** Self-reported health, psychological symptoms, musculoskelton pain, and quality of life score before and after vitamin D supplementation plus increasing daily dairy products intake

	Prefollow up (n = 13)	Postfollow up (n = 13)	P values*
T. dietary Ca intake, mg/d <sup>a</sup>	275.49 [113.46-414.46]	612.68 [596.98- 692.0]	.009
HADS-Anxiety	11.46 ± 4.56	5.77 ± 3.75	<0.001
HADS-Depression	9.15 ± 3.51	6.15 ± 2.64	0.003
Fatigue	12 (92.3%)	0.0 (0%)	<0.001
Pain severity (NRS)	5.14 ± 1.9	3.09 ± 2.22	0.024
USIQ-QOL score	64.5 ± 22.1	20.2 ± 30.1	<0.001

Data are presented as mean ± SD with except to fatigue (n %). HADS-Anxiety, Hospital Anxiety and Depression Scale subscales score for anxiety; HADS-Depression, Hospital Anxiety and Depression Scale (HADS) subscales score for depression; NRS, Numerical Rating scale; USIQ-QOL, Urgency Severity and Impact Questionnaire for the quality of life.

<sup>a</sup>T. dietary Ca intake, mg/d = Total daily calcium intake, mg/d (dairy + supplement). T. dietary Ca intake levels are presented as medians (interquartile ranges) and compared using the Wilcoxon signed ranks test.

\* $P < 0.05$  is considered statistically significant.

may be a risk factor for development of OAB. Vitamin D status was found as an independent significant predictor of OAB syndrome, with an increase of OAB risk by 44 times in patients with severe vitamin D deficiency.

Supplementation with vitamin D plus increased daily calcium intake has significantly improved OAB symptoms. The benefits were observed in patients who were initially presented with moderate to severe urinary symptoms and among those with mild symptoms as no exacerbation in symptoms was reported. This suggests the wide benefits of vitamin D among different levels of urinary symptoms. The results further support the previous observations that low vitamin D was associated with exacerbation of OAB symptoms, which was relieved by vitamin D replacement.<sup>9</sup> These effects might be mediated partially through the anti-inflammatory action of vitamin D, which was indicated by the significant reduction in erythrocyte sedimentation rate after vitamin D supplements.<sup>9</sup> While others related the role of vitamin D in OAB symptoms to skeletal muscle efficiency especially in detrusor muscle/urothelial function.<sup>7</sup>

In addition to the high prevalence of vitamin D deficiency among patients with OAB, 74.6%, and 85.5% of them experienced fatigue and MSP, respectively, and 61.7% of them had the pain daily. The results of the current study are in concordance with previous findings,<sup>10,17</sup> as subjects

with fatigue and MSP had significantly lower mean of vitamin D levels than those who were pain-free, suggesting that the high prevalence of MSP might be attributed in part to the elevated degree of vitamin D-deficient patients. Vitamin D deficiency was associated with persisting pain related to defective mineralization of bone, myopathy, MSP, heightened central sensitivity upon mechanical stimulation in chronic pain patients,<sup>18</sup> and the growth of muscle fibers.<sup>19</sup> In the current study, vitamin D supplementation plus increased dairy products intake resulted in significant reduction in MSP severity, which was accompanied by significant improvements in self-reported fatigue among psychiatric outpatients. Similar findings were also observed previously.<sup>13</sup>

Subjects who experience chronic pain were more likely to have a higher risk of psychological symptoms.<sup>11</sup> In this study, 52.8% of patients with OAB had anxiety and 43.7% of them had depression. Interestingly, anxiety was correlated positively and significantly ( $P < 0.001$ ) with depression symptoms indicating an interaction between vitamin D, pain, and psychological symptoms.

Our study found that patients with OAB displayed higher levels of anxiety and depressive symptoms as compared with controls. In addition, clinical anxiety (scores,  $\geq 11$ ) increased the risk of OAB by about 14 folds. This finding is consistent in part with previous observations, as anxiety scores were significantly higher in women with dry OAB than in controls and a bidirectional relationship between LUTS and depression and anxiety was found.<sup>20,21</sup> Another national study conducted in the US has found that OAB was associated with higher depression score and lower quality of life score.<sup>4</sup>

These psychological symptoms were significantly reduced by vitamin D supplementation and increased daily calcium intake scores. Earlier studies have elucidated that vitamin D supplementation and increased daily calcium intake can reduce psychological symptoms in the different patient population such as patients with MSP and psychiatric outpatients.<sup>11,13</sup> Up to our knowledge, it is the first time to report that vitamin D replacement and improved calcium intake in patients with OAB is associated with improvements in psychological symptoms and quality of life. This finding may be because of the neuroprotective effect mediated by vitamin D.<sup>22</sup> Interaction of vitamin D with its receptor in the brain changes the expression of multiple factors that are involved in intracellular calcium hemostasis and neurodegeneration.<sup>22,23</sup> This improvement in psychological scores with vitamin D supplements might be clinically significant, as the previous investigation showed that the mean difference in anxiety and depression scores between patients

with OAB and controls is minimal (HADS-A: 4.5 vs 3.3; HADS-D: 3 vs 1.2, respectively).<sup>24</sup>

In agreement with previous findings,<sup>11-13,25</sup> the current study demonstrated that daily calcium intake is inversely correlated with depression score, suggesting a link between calcium intake with the risk of psychological symptoms. A result that might be mediated through the role that calcium plays in nervous system function.<sup>26</sup> Apparently, 45.5% of the patients had less than a quarter of the recommended daily calcium intake (1000-1300 mg/day) for 19 to 70 years old.<sup>27</sup>

The current study is limited by small sample size, which may have influenced the ability to draw conclusions about the subgroup analyses. Increasing the sample size of the matched controls would help in reducing the influence factors other than that of interest. Moreover, patients included were receiving medications for OAB that did not show significant clinical benefits. Other studies that investigate the effect of vitamin D supplement with the initial drug therapy might be warranted. The study was cross-sectional, which prohibits the conclusion of any cause-effect relationships. Vitamin D levels were not measured after follow-up. However, patients were followed regularly to assure adherence to vitamin D intake and recommendations. Also, the follow-up study was a pre-postdesign similar to a previously published study<sup>11,13,23</sup> rather than randomization of the patients to placebo and vitamin D. This is due to logistical difficulties.

Collectively, the current study demonstrated that supplementation with vitamin D and increased daily calcium intake may be beneficial for urinary and psychological symptoms associated with OAB, and may improve the quality of life. The findings reflect the importance of assessment of patients with OAB for vitamin D deficiency and associated symptoms.

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## CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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## REFERENCES

- Henderson E, Drake M. Overactive bladder. *Maturitas*. 2010;66(3):257-262.
- Milsom I, Abrams P, Cardozo L, Roberts RG, Thuroff J, Wein AJ. How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. *BJU Int*. 2001;87(9):760-766.
- Coyne KS, Kaplan SA, Chapple CR, et al. Risk factors and comorbid conditions associated with lower urinary tract symptoms: EpiLUTS. *BJU Int*. 2009;103(suppl 3):24-32.
- Stewart WF, Van Rooyen JB, Cundiff GW, et al. Prevalence and burden of overactive bladder in the United States. *World J Urol*. 2003;20(6):327-336.
- Milsom I, Kaplan SA, Coyne KS, Sexton CC, Kopp ZS. Effect of bothersome overactive bladder symptoms on health-related quality of life, anxiety, depression, and treatment seeking in the United States: results from EpiLUTS. *Urology*. 2012;80(1):90-96.
- Lai HH, Rawal A, Shen B, Vetter J. The relationship between anxiety and overactive bladder or urinary incontinence symptoms in the clinical population. *Urology*. 2016;98:50-57.
- Parker-Autry CY, Burgio KL, Richter HE. Vitamin D status: a review with implications for the pelvic floor. *Int Urogynecol J*. 2012;23(11):1517-1526.
- Elshazly MA, Sultan MF, Aboutaleb HA, et al. Vitamin D deficiency and lower urinary tract symptoms in males above 50 years of age. *Urol Ann*. 2017;9(2):170-173.
- Yoo S, Oh S, Kim HS, et al. Impact of serum 25-OH vitamin D level on lower urinary tract symptoms in men: a step towards reducing overactive bladder. *BJU Int*. 2018;122(4):667-672.
- McCabe PS, Pye SR, Beth JM, et al. Low vitamin D and the risk of developing chronic widespread pain: results from the European male ageing study. *BMC Musculoskelet Disord*. 2016;17:32.
- Abdul-Razzak KK, Almanasrah SO, Obeidat BA, Khasawneh AG. Vitamin D is a potential antidepressant in psychiatric outpatients. *Int J Clin Pharmacol Ther*. 2018;56:585-596.
- Alkhatatbeh MJ, Abdul-Razzak KK, Amara NA, Al-Jarrah M. Non-cardiac chest pain and anxiety: a possible link to vitamin D and calcium. *J Clin Psychol Med Settings*. 2018. <https://doi.org/10.1007/s10880-018-9579-2>
- Abdul-Razzak KK, Mayyas FA, Al-Farras MI. Vitamin D as potential antidepressant in outpatients with musculoskeletal pain. *Int J Clin Pharmacol Ther*. 2018;56(9):400-410.
- Lowenstein L, FitzGerald MP, Kenton K, et al. Evaluation of urgency in women, with a validated Urgency, Severity and Impact Questionnaire (USIQ). *Int Urogynecol J Pelvic Floor Dysfunct*. 2009;20(3):301-307.
- Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. 1983;67(6):361-370.
- Crescioli C, Morelli A, Adorini L, et al. Human bladder as a novel target for vitamin D receptor ligands. *J Clin Endocrinol Metab*. 2005;90(2):962-972.
- McBeth J, Pye SR, O'Neill TW, et al. Musculoskeletal pain is associated with very low levels of vitamin D in men: results from the European Male Ageing Study. *Ann Rheum Dis*. 2010;69(8):1448-1452.
- Shipton EE, Shipton EA. Vitamin D deficiency and pain: clinical evidence of low levels of vitamin D and supplementation in chronic pain states. *Pain Ther*. 2015;4(1):67-87.

19. Muir SW, Montero-Odasso M. Effect of vitamin D supplementation on muscle strength, gait and balance in older adults: a systematic review and meta-analysis. *J Am Geriatr Soc*. 2011;59(12):2291-2300.
20. Knight S, Luft J, Nakagawa S, Katzman WB. Comparisons of pelvic floor muscle performance, anxiety, quality of life and life stress in women with dry overactive bladder compared with asymptomatic women. *BJU Int*. 2012;109(11):1685-1689.
21. Martin S, Vincent A, Taylor AW, et al. Lower urinary tract symptoms, depression, anxiety and systemic inflammatory factors in men: a population-based cohort study. *PLoS One*. 2015;10(10):e0137903.
22. Iacopetta K, Collins-Praino LE, Buisman-Pijlman FTA, Liu J, Hutchinson AD, Hutchinson MR. Are the protective benefits of vitamin D in neurodegenerative disease dependent on route of administration? A systematic review. *Nutr Neurosci*. 2018;1-30. <https://doi.org/10.1080/1028415X.2018.1493807>
23. Carroll D, Ring C, Suter M, Willemsen G. The effects of an oral multivitamin combination with calcium, magnesium, and zinc on psychological well-being in healthy young male volunteers: a double-blind placebo-controlled trial. *Psychopharmacology*. 2000;150(2):220-225.
24. Vrijens D, Marcelissen T, Drossaerts J, et al. Self-consciousness/awareness and bladder sensations: comparative study of overactive bladder patients and healthy volunteers. *Low Urin Tract Symptoms*. 2017;11:3-7.
25. Bae YJ, Kim SK. Low dietary calcium is associated with self-rated depression in middle-aged Korean women. *Nutr Res Pract*. 2012;6(6):527-533.
26. Berridge MJ. Dysregulation of neural calcium signaling in Alzheimer disease, bipolar disorder and schizophrenia. *Prion*. 2013;7(1):2-13.
27. Lima GA, Lima PD, Barros Mda G, et al. Calcium intake: good for the bones but bad for the heart? An analysis of clinical studies. *Arch Endocrinol Metab*. 2016;60(3):252-263.

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