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Impact of serum 25-OH vitamin D level on lower urinary tract symptoms in men: a step towards reducing overactive bladder

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Objectives

To evaluate the impact of serum vitamin D level on male lower urinary tract symptoms (LUTS).

Patients and Methods

Men with LUTS who visited the outpatient clinic of the urology department at one of two hospitals between March 2014 and April 2017 were eligible for inclusion in the study. The impact of vitamin D on LUTS was evaluated using multivariate analysis to adjust for age, body mass index, prostate-specific antigen, testosterone, glycated haemoglobin, physical activity and prostate volume. To exclude the effect of seasons, we also analysed the impact during each season.

Results

Vitamin D level was lowest in winter. According to the International Prostate Symptom Score (IPSS) and Overactive Bladder Symptom Score (OABSS), the severity of LUTS peaked in winter. There were no seasonal differences between prostate volume, maximum urinary flow rate (Q_{max}) and post-void residual urine volume (PVR). For all patients, multivariate analysis showed that lower vitamin D level was significantly associated with higher total OABSS, whereas it was not associated with prostate volume, Q_{max}, PVR or total IPSS. In winter, lower vitamin D level was significantly associated with higher total OABSS based on multivariate analysis, whereas it was not during other seasons. In patients with vitamin D deficiency, the total OABSS significantly decreased after vitamin D replacement. The greatest improvement in total OABSS was associated with lower pre-treatment total OABSS and higher post-treatment vitamin D level.

Conclusions

Vitamin D deficiency in men with LUTS may play a role in aggravated overactive bladder (OAB) symptoms, especially in winter. Increasing vitamin D level in patients with vitamin D deficiency appears to alleviate OAB symptoms.

Keywords

overactive, prostatic hyperplasia, seasons, urinary bladder, vitamin D

Introduction

In a previous population-based study, LUTS were reported to be present in approximately half of all adult men [1]. Although most men with mild LUTS do not need to be medically or surgically treated, LUTS have been reported to have detrimental effects on quality of life [2] and the attempt to mitigate them is associated with high socio-economic costs [3].

The causes of LUTS are multifactorial [4], with BPH and overactive bladder (OAB) being the most well-known causes of male LUTS [5]. To prevent the occurrence of LUTS and reduce their severity, the relationship between various micronutrients and BPH or OAB has been widely assessed [6,7], and serum vitamin D has recently been the focus of attention in relation to these conditions. In a previous study, serum vitamin D concentration was reported to be lower in men with LUTS than in men without LUTS [8]. In addition, several studies have reported that prostate volume [9,10] and detrusor overactivity [11] increase as serum vitamin D levels decrease; however, these relationships are still unclear, and more research in these areas is needed to demonstrate the relationship between vitamin D and the aetiologies of male LUTS.

Because both LUTS and vitamin D level are influenced by various factors, these factors should be adjusted for in order

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to identify accurately any relationship between LUTS and vitamin D level. Season is one of the key factors affecting both vitamin D level and LUTS. Although serum vitamin D levels may be lower in winter, the season during which LUTS are reportedly aggravated [12], there is a lack of data on the influence of season on the relationship between vitamin D and LUTS. In the present study, we tried to determine if vitamin D level has a role in male LUTS, while considering seasonal effects. Additionally, we evaluated if vitamin D replacement could alleviate LUTS in men with both LUTS and vitamin D deficiency.

Patients and Methods

Study Cohort

Men with LUTS who visited the outpatient clinic of the urology department at one of two hospitals between March 2014 and April 2017 were initially eligible for inclusion in the present study. We prospectively enrolled 457 consecutive patients who agreed to evaluation of their serum 25-OH vitamin D levels after explanation of the study objectives. Exclusion criteria included patients with a history of urological surgery, any urological malignancies, neurological or debilitating disease, recurrent UTI, and those taking any medication that might affect LUTS or any vitamin D preparations. After excluding 23 patients for whom complete data were not available, 434 patients were finally included in the analysis. This study was approved by our hospital's institutional review board.

Patient Evaluation

Initial patient evaluation included medical history acquisition, physical examination and the completion of validated questionnaires, such as the IPSS, the Overactive Bladder Symptom Score (OABSS), and the International Physical Activity Questionnaire (I-PAQ). Additionally, laboratory test data, including serum anti-inflammatory markers, serum PSA testosterone and glycated haemoglobin (HbA1c) levels, urine analysis, uroflowmetry, with post-void residual urine volume (PVR) and prostate volume measurement using TRUS, were obtained. Serum 25-OH vitamin D level was assessed in all patients using a chemiluminescent protein binding assay. Serum testosterone level was evaluated between 08:00 and 11:00 h.

Definitions

Seasons were classified as follows: spring, March to May; summer, June to August; autumn, September to November; and winter, December to February, based on the year-round change in degree of ultraviolet light (Fig. S1). Vitamin D deficiency was defined as serum 25-OH vitamin D level <20 ng/mL, and vitamin D insufficiency was defined as 25-OH vitamin D level ≥20 and <30 ng/mL [13]. According to the total IPSS, LUTS severity was divided into three groups as follows: mild, ≤7; moderate, 8–19; and severe, ≥20 [14]. The diagnostic criteria for OAB were: OABSS question 3 score ≥2 and total OABSS of ≥3. According to total OABSS, OAB severity was categorized as follows: mild, ≤5 and moderate to severe, ≥6) [15]. Bladder voiding efficiency was calculated using the following formula: bladder voiding efficiency = voided volume/(voided volume + PVR) × 100 [16]. Estimated weekly metabolic equivalent of task (MET) min were calculated based on the total weekly activity assessed by the I-PAQ and calculated using the following formula: MET min/week = METs based on the intensity (if walking: 3.3, if moderate intensity activity: 4.0, if vigorous intensity activity: 8.0) × min × frequency per week [17].

Treatment of Vitamin D Deficiency

Patients with vitamin D deficiency received an i.m. injection of cholecalciferol, administered as 200 000 IU in a single dose, if they consented to the treatment. Vitamin D replacement was considered if patients had vitamin D deficiency and any symptoms of vitamin D deficiency, including mild swelling or weakness. I.m. single injection was selected because of concern about adherence to treatment and patient convenience. In addition, these patients did not take any medication such as anti-muscarinic agents or β3-adrenergics for at least 2 months after vitamin D replacement. At 2 months after treatment, follow-up measures included assessments of the IPSS, OABSS, I-PAQ, serum 25-OH vitamin D level, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) level.

Statistical Analysis

Patient characteristics were presented and compared according to the groups using the mean ± SD for continuous variables and a frequency table for categorical variables. Multivariate linear regression analysis was performed to assess the impact of serum 25-OH vitamin D level on the evaluation parameters for LUTS after adjusting for other variables including age, body mass index (BMI), serum PSA level, serum testosterone level, serum HbA1c level, physical activity and prostate volume. Serum 25-OH vitamin D level was calculated and compared according to the OAB symptom severity and season. In addition, the impacts of serum 25-OH vitamin D level on the OABSS were separately assessed for each season after adjusting for other variables. The relationship between total OABSS and serum inflammatory markers was also examined. The improvement in OABSS after vitamin D replacement was calculated, in addition to changes in serum 25-OH vitamin D, ESR and CRP levels. In addition, the correlation coefficient between the improvement in the OABSS and pre- and post-treatment variables was assessed. All statistical comparisons were performed using IBM SPSS Statistics, Version 21 (IBM SPSS, Armonk, NY, USA). A *P* value of <0.05 was considered statistically significant.

Results

Among 434 patients, 119 patients had their serum 25-OG vitamin D level evaluated during spring, 111 patients during summer, 70 patients during autumn, and 134 patients during winter (Table 1). The mean serum 25-OH vitamin D levels were 17.4, 24.9, 20.0 and 16.3 ng/mL in spring, summer, autumn and winter, respectively ($P < 0.001$). A higher percentage of patients with vitamin D deficiency were observed in winter (68.1% in spring vs 30.6% in summer vs 55.7% in autumn vs 75.4% in winter; $P < 0.001$). Although patient ages were not equivalent (56.8 vs 59.0 vs 61.4 vs 60.2 years; $P = 0.026$), other patient characteristics, including prostate volume, maximum urinary flow rate (Q_{max}) and PVR were similar among the four seasons; however, the percentages of patients with severe LUTS (28.1% [spring] vs 29.1% [summer] vs 28.4% [autumn] vs 33.3% [winter]; $P = 0.048$), and moderate-to-severe OAB (31.0% vs 31.4% vs 35.8% vs 47.7%; $P = 0.042$) were highest in winter. In addition, the quality of life index (3.3 vs 3.6 vs 3.3 vs 3.9, $P = 0.009$) was highest in winter.

According to multivariate analysis, after adjusting for other variables such as age, BMI, serum PSA, serum testosterone, serum HbA1c and prostate volume, serum 25-OH vitamin D level was not associated with prostate volume, Q_{max}, PVR or total IPSS (Table 2); however, a lower serum 25-OH vitamin D level (B: −0.040, $P = 0.037$) was significantly associated with a higher total OABSS, in addition to older age, a higher serum PSA level and a higher HbA1c level. During winter, serum 25-OH vitamin D levels significantly decreased as OAB symptom severity increased (none: 17.9 vs mild: 18.6 vs moderate to severe: 14.7 ng/mL; $P = 0.014$), whereas the same finding was not observed during other seasons (Table 3). On multivariate analysis, after adjusting for other variables, serum 25-OH vitamin D level (B: −0.134, $P = 0.014$) was significantly associated with total OABSS in winter, while it was not associated with OABSS during other seasons (Table 4).

Table 1 Voiding-related variables and vitamin D level according to season.

	Spring	Summer	Autumn	Winter	*P*
Patients, *n* (%)	119 (27.4)	111 (25.6)	70 (16.1)	134 (31.0)	
Mean ± SD age, years	56.8 ± 11.3	59.0 ± 11.6	61.4 ± 11.2	60.2 ± 11.3	0.026
Mean ± SD BMI, kg/m^2	24.7 ± 3.1	24.8 ± 3.2	24.7 ± 3.4	24.9 ± 4.1	0.924
Diabetes, *n* (%)	23 (19.3)	24 (21.6)	7 (10.0)	22 (16.4)	0.220
Hypertension, *n* (%)	33 (27.7)	45 (40.5)	20 (28.6)	44 (32.8)	0.173
Mean ± SD MET, min/week	2 504 ± 5 428	2 054 ± 3 378	2 622 ± 4 023	2 777 ± 8 343	0.813
Mean ± SD PSA, ng/mL	1.8 ± 2.5	2.4 ± 5.1	2.1 ± 2.4	3.1 ± 6.6	0.193
Mean ± SD testosterone, ng/mL	4.9 ± 1.8	4.6 ± 1.9	4.9 ± 2.3	4.7 ± 1.9	0.586
Mean ± SD HbA1c, (%)	6.0 ± 1.3	5.9 ± 0.8	6.0 ± 1.4	6.0 ± 1.1	0.951
Mean ± SD ESR, mm/h	10.4 ± 10.0	9.2 ± 11.3	10.3 ± 11.3	9.0 ± 8.2	0.618
Mean ± SD CRP, mg/L	0.17 ± 0.35	0.26 ± 0.75	0.25 ± 0.53	0.14 ± 0.24	0.163
Urine analysis, *n* (%)					
Haematuria	10 (8.4)	2 (1.9)	5 (7.2)	4 (3.0)	0.071
Pyuria	2 (1.7)	5 (4.7)	5 (7.2)	6 (4.6)	0.314
Nitrite (+)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0.524
Mean ± SD prostate volume	23.4 ± 10.8	24.5 ± 11.4	25.1 ± 8.8	27.1 ± 13.6	0.116
Mean ± SD uroflowmetry variables					
Q_{max}, mL/s	14.2 ± 7.4	14.5 ± 7.8	13.0 ± 7.3	14.8 ± 9.4	0.541
Voided volume, mL	254.4 ± 178.3	245.1 ± 148.3	184.9 ± 135.7	230.0 ± 179.3	0.056
PVR, mL	15.9 ± 19.0	29.4 ± 52.0	29.2 ± 42.0	20.7 ± 41.0	0.062
IPSS, *n* (%)					
Mild	36 (31.6)	29 (28.2)	15 (22.4)	17 (13.5)	0.048
Moderate	46 (40.4)	44 (42.7)	33 (49.3)	67 (53.2)	
Severe	32 (28.1)	30 (29.1)	19 (28.4)	42 (33.3)	
Mean ± SD quality of life index	3.3 ± 1.6	3.6 ± 1.5	3.3 ± 1.5	3.9 ± 1.3	0.009
OABSS, *n* (%)					
None	59 (52.2)	62 (59.0)	32 (47.8)	54 (42.2)	0.042
Mild	19 (16.8)	10 (9.5)	11 (16.4)	13 (10.2)	
Moderate to severe	35 (31.0)	33 (31.4)	24 (35.8)	61 (47.7)	
25-OH-vitamin D level, *n* (%)					
Normal	7 (5.9)	32 (28.8)	8 (11.4)	5 (3.7)	<0.001
Insufficiency	31 (26.1)	45 (40.5)	23 (32.9)	28 (20.9)	
Deficiency	81 (68.1)	34 (30.6)	39 (55.7)	101 (75.4)	

BMI, body mass index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HbA1c, glycated haemoglobin; OABSS, Overactive Bladder Symptom Score; PVR, post-void residual urine volume; Q_{max}, maximum urinary flow rate.

Table 2 Multivariate analysis for predicting objective and subjective variables for male LUTS.

Variables	B	95% CI		*P*
		Lower	Upper	
Prostate volume				
Age	0.302	0.184	0.421	<0.001
BMI	0.861	0.439	1.282	<0.001
PSA	0.561	0.262	0.859	<0.001
Q_{max}				
Age	−0.242	−0.325	−0.158	<0.001
BMI	0.385	0.086	0.685	0.012
HbA1c	−1.026	−1.884	−0.169	0.019
PVR				
Age	0.788	0.391	1.186	<0.001
Total IPSS				
BMI	−0.405	−0.738	−0.071	0.018
HbA1c	1.363	0.400	2.326	0.006
Prostate volume	0.116	0.030	0.202	0.009
Total OABSS				
Age	0.050	0.015	0.085	0.005
PSA	0.091	0.008	0.174	0.031
HbA1c	0.386	0.043	0.728	0.028
25-OH-vitamin D level	−0.040	−0.077	−0.002	0.037

BMI, body mass index; HbA1c, glycated haemoglobin; OABSS, Overactive Bladder Symptom Score; PVR, post-void residual urine volume; Q_{max}, maximum urinary flow rate.

Table 3 Relationship between overactive bladder symptom severity and 25-OH-vitamin D level according to season.

	None	Mild	Moderate to severe	*P*
Spring	17.7 ± 7.2	16.5 ± 8.6	16.8 ± 6.5	0.753
Summer	24.4 ± 12.4	25.1 ± 9.7	26.1 ± 9.3	0.780
Autumn	20.5 ± 8.2	20.2 ± 6.0	19.6 ± 10.0	0.931
Winter	17.9 ± 7.2	18.6 ± 6.1	14.7 ± 5.6	0.014

Table 4 Impact of 25-OH-vitamin D level on Overactive Bladder Symptom Score according to season after adjusting age, body mass index, PSA, testosterone, glycated haemoglobin and prostate volume.

Season	B	95% CI		*P*
		Lower	Upper	
Spring	0.009	−0.081	0.099	0.855
Summer	−0.029	−0.093	0.035	0.074
Autumn	−0.008	−0.106	0.090	0.870
Winter	−0.134	−0.241	−0.027	0.014

As total OABSS increased, serum ESR level significantly increased (r = 0.137, P = 0.006; Table S1). In 40 patients with vitamin D deficiency who received vitamin D replacement, serum ESR level (10.4 vs 5.8 mm/h; P = 0.007) significantly decreased after treatment (Table 5). In these patients, total OABSS significantly decreased 2 months after vitamin D replacement (3.7 vs 2.4; P = 0.015), and serum 25-OH vitamin D level significantly increased (pre-treatment: 13.7 vs post-treatment: 25.3 ng/mL; P < 0.001 [Table 5]). The improvement in total OABSS after vitamin D replacement was significantly associated with a lower pre-treatment total OABSS (r = −0.744, P < 0.001) and higher post-treatment total serum 25-OH vitamin D level (r = 0.357, P = 0.042; Table S2).

Discussion

Recently, it has been suggested that a relationship exists between serum vitamin D level and LUTS [7,18]; however, as LUTS and their causes are closely interrelated, a detailed study on whether vitamin D level affects LUTS or its causes is required. In addition, these relationships should be assessed after adjusting for seasonal effects as season affects serum vitamin D levels and LUTS. In the present study, we showed that decreased serum 25-OH vitamin D level plays a role in OAB, particularly in winter, but not in BPH, after adjusting for other variables.

During winter, LUTS, assessed according to the IPSS and OABSS, worsened and the quality-of-life index score also decreased, which is consistent with the results of a previous study [12]. In addition, serum 25-OH vitamin D level decreased in winter, as expected, because the amount of vitamin D synthesis is affected by skin exposure to solar ultraviolet B light. In other words, to assess accurately the role of 25-OH vitamin D level on LUTS, the season during which the evaluation took place needed to be considered. To date, there has been a lack of data, however, on the influence of season on the relationship between vitamin D and LUTS. To our knowledge, this is the first study to evaluate the impact of vitamin D level on male LUTS after considering the season during which the evaluation of serum vitamin D level occurred. In this regard, we believe this study will be useful for clinicians, especially for those who work in temperate climate zones where there are four distinct seasons.

In the present study, before adjusting for the season at evaluation, serum 25-OH vitamin D level was significantly associated with total OABSS, a result which is in accordance with previous studies [11,19]. Interestingly, when multivariate analysis was performed for each season, the decrement in 25-OH vitamin D level was a significant variable for severe OAB, but only during winter. These results might come from the worsened OAB symptoms attributable to cold weather and the low mean vitamin D level during winter. Irritable bladder attributable to cold weather could induce an inflammatory reaction [20], and vitamin D could play an important role in this situation. In other words, in patients with vitamin D deficiency, OAB symptoms attributable to cold weather in winter could gradually worsen without improvements because of the decreased anti-inflammatory effects of vitamin D level. Nevertheless, the conclusion that serum vitamin D level was not associated with LUTS during other seasons should not be drawn because, as mentioned above, vitamin D level was inversely correlated with LUTS during all seasons, although

Table 5 Improvements in Overactive Bladder Symptom Score after vitamin D replacement in patients with vitamin D deficiency.

	Pretreatment	Post-treatment	Difference	95% CI		P
				Lower	Upper	
25-OH-vitamin D level, ng/mL	13.7 ± 3.6	25.3 ± 8.6	11.6	9.1	14.2	<0.001
OABSS	3.7 ± 3.0	2.4 ± 1.8	−1.3	−2.4	−0.3	0.015
ESR, mm/h	10.4 ± 10.0	5.8 ± 3.4	−4.6	−7.8	−1.3	0.007
CRP, mg/L	0.2 ± 0.4	0.2 ± 0.7	−0.0	−0.3	0.3	0.937

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; OABSS, Overactive Bladder Symptom Score.

statistical significance was not achieved. As a result, we can only conclude that OAB symptom aggravation might be affected by decreased serum vitamin D levels, especially during winter. Because both low serum vitamin D level and cold weather are thought to affect the severity of OAB in winter, however, the effects of each factor on the severity of OAB should be compared in future studies.

According to previous studies, vitamin D replacement could be recommended as a possible treatment option for LUTS, although most of these studies were performed in women [21,22]. In the present study, vitamin D replacement was shown to improve OAB symptoms 2 months after i.m. cholecalciferol infusion in men with vitamin D deficiency. In these patients, ESR level, which was significantly associated with the pretreatment total OABSS, was significantly decreased after vitamin D replacement. Based on these results, we can hypothesize that vitamin D replacement might improve OAB symptoms through its anti-inflammatory action. This anti-inflammatory action is thought to mainly affect chronic inflammation because serum CRP level, which reflects acute inflammation, did not decrease after vitamin D replacement. A previous study reporting the association between an inflammatory marker and LUTS appears to support these results [23]. In addition, the effects of vitamin D replacement on the improvement of the OAB symptoms seem to be increased as the pre-treatment OABSS decreased and post-treatment vitamin D level increased, although multivariate analysis could not be performed because of the small number of patients who received treatment. In other words, vitamin D supplementation and/or lifestyle modification, such as increased outdoor activity with exposure to sunshine, could be considered in patients with mild OAB and vitamin D deficiency. As it is controversial to recommend vitamin D intake for healthy people in winter [24], encouraging sunlight exposure might be the best way to increase serum 25-OH vitamin D level for patients in this clinical situation. In general, regular, short exposure to sunlight with unprotected skin is reported to be the best way for the body to synthesize vitamin D by sunlight exposure [25]; therefore, these methods could be recommended for these patients.

Based on the present study, objective measures, including prostate volume, Q_{max} and PVR were not associated with serum vitamin D level, nor was total IPSS. In a previous study, low vitamin D level was reported to be associated with BPH [26], which is not consistent with the results of the present study. These outcome differences might result from racial differences or differences in weather throughout the year. The lower vitamin D levels observed in the present study compared with those of other studies could be another reason [26,27]; however, because the studies aimed to assess the relationship between vitamin D level and objective variables showed contrasting results, this relationship needs to be further elucidated in future studies involving measurement of serial follow-up serum vitamin D levels around the year.

The present study has several limitations. First, it included a small number of patients, although other similar studies have generally included fewer patients than the present study. Second, although physical activity was assessed by the I-PAQ, information regarding the duration of sunlight exposure, which is thought to be essential for vitamin D synthesis, was not collected in this study. Despite the small cohort, given the promising treatment outcomes after vitamin D replacement in patients with vitamin D deficiency, our findings suggest a therapeutic strategy could be to restore serum vitamin D level to alleviate OAB symptoms. Additionally, because OAB is a common condition in men [28], our findings could be helpful for a great number of adult men with OAB, especially in winter.

In conclusion, our data indicate that low serum vitamin D levels in men with LUTS may be involved in aggravated OAB symptoms, especially in winter, while such low levels do not appear to be associated with BPH. Moreover, elevated vitamin D levels in patients with vitamin D deficiency showed promising results for improving OAB symptoms. Further studies with a larger number of patients are needed to validate our findings.

Conflict of Interest

None declared.

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Abbreviations: BMI, body mass index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HbA1c, glycated haemoglobin; I-PAQ, International Physical Activity Questionnaire; MET, metabolic equivalent of task; OAB, overactive bladder; OABSS, Overactive Bladder Symptom Score; PVR, post-void residual urine volume; Q_{max}, maximum urinary flow rate.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article:

Figure S1. Year-round changes in ultraviolet index and vitamin D level (Spring; March to May, Summer; June to August, Autumn; September to November, Winter: December to February.
Table S1. The relationship between OABSS and inflammatory markers.
Table S2. Variables related with the improvement in OABSS.