



Low Serum 25-Hydroxyvitamin D Level as a Potential Risk Factor of Erectile Dysfunction in Elderly Men with Moderate to Severe Lower Urinary Tract Symptoms

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Purpose: To evaluate the correlation between vitamin D level and erectile dysfunction (ED) in male lower urinary tract symptoms (LUTS) patients.

Materials and Methods: We analyzed data from 534 male patients who were tested for LUTS from 2014 to 2017. LUTS severity was classified into mild (≤ 7) or moderate to severe (≥ 8) based on total IPSS scores. Vitamin D deficiency was defined as a serum 25-hydroxyvitamin D [25(OH)D] level of less than 20 ng/mL. The severity of ED was dichotomized into mild (≥ 17 points) or moderate to severe (≤ 16 points) depending on total IIEF-5 scores. The association of the serum 25(OH)D level with moderate to severe ED was assessed using logistic regression analysis.

Results: In the entire cohort, moderate to severe ED was significantly associated with age ≥ 60 years (odds ratio [OR], 1.762; 95% confidence interval [CI], 1.011–3.073) and moderate to severe LUTS (OR, 2.075; 95% CI, 1.134–3.789), but not with serum 25(OH)D level (OR, 1.001; 95% CI, 0.979–1.023). Whereas, in the subgroup consisting of moderate to severe LUTS patients over 60 years ($n=223$), either low serum 25(OH)D level (OR, 0.944; 95% CI, 0.903–0.986) or vitamin D deficiency (OR, 2.949; 95% CI, 1.118–7.782) was the independent risk factor of moderate to severe ED as a result of each multivariate analysis.

Conclusions: Low vitamin D status closely correlated with moderate to severe ED in elderly men with moderate to severe LUTS.

Keywords: Erectile dysfunction; Lower urinary tract symptoms; Vitamin D deficiency; 25-hydroxyvitamin D

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INTRODUCTION

Lower urinary tract symptoms (LUTS) and erectile dysfunction (ED) have shown an increasing global

prevalence and are significant health problems that can adversely impact the quality of life of the male population [1-3]. The prevalence of both disease entities presents an age-dependent trend. In the case of LUTS,

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prevalence increases from 10.5% at age 30–39 years to 25.5% at age 70–79 years (usually with benign prostatic hyperplasia [BPH] in men), and about 70% of adult men may have experienced at least one LUTS episode during their lifetime [2-4]. A similar increase in prevalence has also been observed in ED, from 6.5% in men aged 20–39 years to 77.5% in those aged 75 years and above, and it is estimated that 322 million men may be affected by ED in 2025 [1,5]. In addition, both conditions share common risk factors such as hypertension, diabetes mellitus, and dyslipidemia [6]. Based on these findings, there have been several studies that suggest a close relationship between LUTS and ED [6-9].

Despite ED (defined as the inability to obtain and maintain a sufficient erection for satisfactory sexual performance) being a multifactorial disease (neurogenic, psychogenic, and organic causes or a combination of multiple causes), it is primarily a vascular disorder related to an underlying endothelial dysfunction (END). END is a key factor in the pathogenesis of diverse vascular disorders, including atherosclerosis, hypertension, diabetes, coronary artery disease, and ED [10-12]. Therefore, any disorder causing END can interfere with vasodilation, which may result in ED.

Vitamin D, which is a steroid hormone produced in human skin by sunlight exposure, is known to modulate endothelial function by stimulating nitric oxide (NO) production that protects against oxidative stress, preventing endothelial apoptosis [13,14]. Several observational studies have suggested low levels of serum 25-hydroxyvitamin D [25(OH)D], which is a metabolite form of vitamin D within the human body, to be associated with the increased risk of cardiovascular disease (CVD) through established risk factors for vascular END such as atherosclerosis, hypertension, diabetes, and inflammation [15-19]. Given that ED is a vascular disease with a similar mechanism of occurrence (by sharing the identical risk factors with CVD), some studies have reported significant correlations between vitamin D deficiency and ED development [20-24]. Moreover, it has been recently reported that vitamin D deficiency is related to the degree of LUTS that manifests in urologic benign diseases such as BPH and overactive bladder (OAB) [25-27].

To our knowledge, no studies have evaluated a possible association between vitamin D and ED in male patients with LUTS. Hence, in this study, we sought to investigate the relationship between serum vitamin D

status and ED severity in a cohort consisting of male LUTS patients.

MATERIALS AND METHODS

1. Ethics statement

Before the initiation of the study, the use of patients' information in this study was approved from institutional review board (IRB) of Dongguk University Ilsan Hospital (IRB number: DUIH-2015-79) and Seoul Metropolitan Government-Seoul National University (SMG-SNU) Boramae Medical Center (IRB number: H-10-2016-79). Because of the retrospective nature of this study, the need for receiving written informed consent from each patient was exempted from the IRB of each institution.

2. Study population and design

The use of patient data was approved by the IRB of Dongguk University Ilsan Hospital and SMG-SNU Boramae Medical Center prior to study initiation. All patient data and records were anonymized before analysis. All study protocols were prepared in compliance with the Declaration of Helsinki. Among men who visited our hospital because of LUTS between 2014 and 2017, a total of 570 male patients who agreed to the evaluation of serum 25(OH)D levels after being informed of the study objectives were included in this study. The exclusion criteria were as follows: a history of prostate or bladder cancers, neurological disorders, urological surgery, current urinary tract infection, and patients taking any medications for LUTS or vitamin D insufficiency. Consequently, after excluding 36 subjects owing to incomplete data, a total of 534 patients were eligible for the final analysis.

3. Evaluation and definitions

To determine the association of vitamin D deficiency with ED in men with LUTS, the patients were evaluated for medical history, physical examination, blood tests, urinalysis, uroflowmetry, post-voided residual (PVR), several questionnaires such as the International Prostate Symptom Score (IPSS) and the International Index of Erectile Function-5 (IIEF-5), and transrectal ultrasound. The demographic variables were as follows: age (<60 y *vs.* ≥60 y), body mass index (BMI), presence or absence of hypertension, diabetes mellitus, and dyslipidemia. Age was dichotomized according to the

Table 1. Baseline characteristics of the entire cohort (n=534) and comparative analytic results according to LUTS severity

Variable	Total (n=534)	Mild (IPSS total score ≤7) (n=114)	Moderate to severe (IPSS total score ≥8) (n=420)	p-value
Demographic parameters				
Age (y)	60.1±10.8	58.1±11.3	60.6±10.6	0.033
<60	260 (48.7)	63 (55.3)	197 (46.9)	0.139
≥60	274 (51.3)	51 (44.7)	223 (53.1)	
Body mass index (kg/m ²)	24.7±3.5	25.0±3.5	24.6±3.5	0.334
Normal (18.5–22.9)	158 (29.6)	31 (27.9)	127 (30.7)	0.692
Overweight (23.0–24.9)	140 (26.2)	28 (25.2)	112 (27.1)	
Obese (≥25.0)	227 (42.5)	52 (46.8)	175 (42.3)	
Missing/unknown	9 (1.7)			
Hypertension				
No	351 (65.7)	85 (75.2)	266 (63.6)	0.025
Yes	180 (33.7)	28 (24.8)	152 (36.4)	
Missing/unknown	3 (0.6)			
Diabetes mellitus				
No	440 (82.4)	93 (83.0)	347 (82.8)	>0.999
Yes	91 (17.0)	19 (17.0)	72 (17.2)	
Missing/unknown	3 (0.6)			
Dyslipidemia				
No	480 (89.9)	99 (89.2)	381 (91.1)	0.580
Yes	49 (9.2)	12 (10.8)	37 (8.9)	
Missing/unknown	5 (0.9)			
IIEF-5 total score	12.8±7.5	14.7±7.7	12.3±7.4	0.009
Mild (≥17 scores)	140 (26.2)	42 (46.7)	98 (31.6)	0.012
Moderate to severe (≤16 scores)	260 (48.7)	48 (53.3)	212 (68.4)	
Missing/unknown	134 (25.1)			
Hematological parameters				
PSA (ng/mL)	2.29±4.46	1.45±1.41	2.51±4.95	<0.005
Serum hemoglobin (g/dL)	14.6±1.3	14.8±1.3	14.5±1.3	0.037
Serum creatinine (mg/dL)	0.91±0.21	0.92±0.15	0.92±0.22	0.966
eGFR (mL/min/1.73 m ²)	90.1±31.9	89.7±13.6	88.8±16.1	0.588
Total cholesterol (mg/dL)	177.2±38.2	183.7±40.6	175.5±37.4	0.048
Serum albumin (g/dL)	4.3±0.3	4.4±0.3	4.3±0.3	0.008
HbA1c (%)	5.9±1.0	5.9±0.9	5.9±1.0	0.501
Serum testosterone (ng/mL)	4.75±1.99	4.64±2.06	4.78±1.97	0.535
ESR (mm/h)	9.6±12.3	10.2±9.9	9.4±12.9	0.550
CRP (mg/dL)	0.45±1.38	0.43±1.39	0.46±1.37	0.854
Serum 25(OH)D level	19.9±9.1	20.5±9.1	19.8±9.1	0.464
No vitamin D deficiency	226 (42.3)	48 (42.9)	178 (44.1)	0.831
Vitamin D deficiency	290 (54.3)	64 (57.1)	226 (55.9)	
Missing/unknown	18 (3.4)			
Urination-related parameters				
Qmax (mL/sec)	13.6±7.9	16.1±7.8	13.0±7.8	0.001
Voided volume (mL)	219.8±160.6	251.7±165.9	212±158.6	0.037
PVR (mL)	23.3±44.6	14.9±15.3	25.2±48.9	0.001
Voiding efficiency (%)	87.7±0.2	91.0±0.1	86.8±0.2	0.022
Prostate volume (mL)	26.0±11.6	23.7±8.5	26.6±12.2	0.009

Values are presented as mean±standard deviation or number (%).

LUTS: lower urinary tract symptoms, IPSS: International Prostate Symptom Score, IIEF-5: International Index of Erectile Function-5, PSA: prostate-specific antigen, eGFR: estimated glomerular filtration rate, HbA1c: hemoglobin A1c, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, 25(OH)D: 25-hydroxyvitamin D, Qmax: maximal urinary flow rate, PVR: post-voided residual.

mean value of 60 years. According to the Asian BMI cutoffs, BMI was classified into normal (18.5–22.9 kg/m²), overweight (23.0–24.9 kg/m²), and obese (≥25.0 kg/m²) groups [28]. Blood tests included prostate-specific antigen (PSA), serum hemoglobin, serum creatinine level, estimated glomerular filtration rate (eGFR), total cholesterol, serum albumin, hemoglobin A1c (HbA1c), serum testosterone, erythrocyte sedimentation rate, C-reactive protein, and serum 25(OH)D levels. Owing to serum 25(OH)D being a parameter that reflects the level of vitamin D in the body, vitamin D deficiency was defined as a case where serum 25(OH)D level was less than 20 ng/mL. The serum level of 25(OH)D was determined using a chemiluminescent protein binding assay. The severity of LUTS was determined by the total sum of each IPSS sub-score and was subsequently divided into mild (≤7), moderate (8–19), and severe (20–35). To facilitate the analysis, the study cohort was dichotomized into mild (≤7) or moderate to severe (≥8) LUTS groups. Urination-related parameters included in the study were as follows: maximal urinary flow rate (Q_{max}), voided volume, PVR, prostate volume, and voiding efficiency. Voiding efficiency (%) was defined as the value of voided volume divided by the voided volume plus PVR. The degree of ED was evaluated based on the total sum of each IIEF-5 sub-score. Following the total IIEF-5 scores, the severity of ED was dichotomized into mild (≥17 points) or moderate to severe (≤16 points).

4. Statistical analysis

The comparison of each variable between two LUTS groups was performed using the chi-squared or Fisher's exact tests for categorical variables and the Student's t-test for continuous variables. Continuous variables were expressed as means and standard deviations and categorical variables were noted as absolute numbers and relative percentages. Univariate and multivariate logistic regression analyses were used to evaluate the factors that were significantly associated with moderate to severe ED. All statistical analyses were performed using SPSS version 21.0 (IBM Corp., Armonk, NY, USA) and two-sided p-values <0.05 were considered to be statistically significant.

RESULTS

1. Baseline characteristics of the study cohort

The characteristics of the study cohort (n=534) and comparative analytic results between the two LUTS groups are summarized in Table 1. The mean age and BMI for the entire cohort were 60.1 years and 24.7 kg/m², respectively. Patients who complained of moderate to severe ED were 260 (48.7%), and vitamin D deficiency was observed in 290 (54.3%) patients. Depending on the total IPSS scores, 114 (21.3%) and 420 (78.7%) patients were assigned to mild (≤7) and moderate to severe (≥8) LUTS groups, respectively. Compared with the mild LUTS group, the moderate to severe LUTS

Table 2. Comparison of erectile function and urination-related parameters in LUTS males with or without vitamin D deficiency

Variable	Vitamin D deficiency (<20 ng/mL)	No vitamin D deficiency (≥20 ng/mL)	p-value
IPSS total scores	15.3±8.6	14.9±8.4	0.622
Mild (≤7)	64 (22.1)	48 (21.2)	0.831
Moderate to severe (≥8)	226 (77.9)	178 (78.8)	
IIEF-5 total scores	12.4±7.9	13.2±7.0	0.283
Mild (≥17 scores)	77 (34.8)	58 (34.9)	1.000
Moderate to severe (≤16 scores)	144 (65.2)	108 (65.1)	
Serum testosterone (ng/mL)	4.64±1.88	4.88±2.14	0.204
PSA (ng/mL)	2.36±4.39	2.21±4.59	0.712
Q _{max} (mL/s)	13.8±7.5	13.4±8.4	0.615
Voided volume (mL)	222.6±165.4	217.3±155.3	0.726
PVR (mL)	23.6±46.9	23.1±41.9	0.899
Voiding efficiency (%)	87.7±0.2	87.6±0.2	0.948
Prostate volume (mL)	25.6±10.9	26.5±12.6	0.443

Values are presented as mean±standard deviation or number (%).

LUTS: lower urinary tract symptoms, IPSS: International Prostate Symptom Score, IIEF-5: International Index of Erectile Function-5, PSA: prostate-specific antigen, Q_{max}: maximal urinary flow rate, PVR: post-voided residual.

group showed lower IIEF-5 total scores, a high frequency of hypertension, a greater frequency of moderate to severe ED, a higher PSA level, older age, and unfavorable urination-related parameters such as lower Q_{max}, lower voided volume, higher PVR, larger prostate volume, and lower voiding efficiency (all p<0.05). Nevertheless, there was no significant difference between serum 25(OH)D level and the distribution of vitamin D deficiency between the two LUTS groups.

2. The association of vitamin D deficiency with erectile dysfunction in men with lower urinary tract symptoms

Table 2 lists the comparative results of the ED- or urination-related parameters according to the presence

or absence of vitamin D deficiency. There were no significant differences in IPSS total scores, LUTS severity, IIEF-5 total scores, ED severity, serum testosterone, PSA level, Q_{max}, voided volume, PVR, voiding efficiency, and prostate volume between the two groups (Table 2).

Multivariate logistic regression analyses conducted in the entire cohort showed that age over 60 years (odds ratio [OR], 1.762; 95% confidence interval [CI], 1.011–3.073), moderate to severe LUTS (OR, 2.075; 95% CI, 1.134–3.789), the presence of hypertension (OR, 1.845; 95% CI, 1.034–3.290), decreased eGFR (OR, 0.980; 95% CI, 0.961–0.999), and higher HbA1c level (OR, 1.889; 95% CI, 1.259–2.835) were the significant related factors to moderate to severe ED, but serum 25(OH)D level and

Table 3. Logistic regression analyses for moderate to severe ED in the entire study cohort (n=534)

Variable	Univariate analysis		Multivariate analysis	
	Unadjusted OR (95% CI)	p-value	Adjusted OR (95%CI)	p-value
Age (continuous)	1.061 (1.039–1.084)	<0.001		
Age (≥60 vs. <60 y)	2.751 (1.785–4.240)	<0.001	1.762 (1.011–3.073)	0.046
Body mass index (continuous)	0.981 (0.925–1.041)	0.527		
Body mass index (ref. normal)				
Overweight	1.398 (0.762–2.489)	0.289		
Obese	0.794 (0.479–1.315)	0.371		
Hypertension (yes vs. no)	2.099 (1.320–3.338)	0.002	1.845 (1.034–3.290)	0.038
Diabetes mellitus (yes vs. no)	3.298 (1.619–6.718)	0.001	0.983 (0.344–2.814)	0.975
Dyslipidemia (yes vs. no)	0.805 (0.412–1.572)	0.526		
IPSS total scores (continuous)	1.037 (1.010–1.066)	0.008		
LUTS severity (moderate to severe vs. mild)	1.893 (1.173–3.054)	0.009	2.075 (1.134–3.789)	0.018
Serum hemoglobin (continuous)	0.790 (0.665–0.939)	0.007	0.842(0.674–1.053)	0.131
ESR (continuous)	1.019 (0.993–1.046)	0.149		
CRP (continuous)	1.064 (0.906–1.249)	0.448		
Serum creatinine (continuous)	2.589 (0.758–8.848)	0.129		
eGFR (continuous)	0.969 (0.954–0.985)	<0.001	0.980 (0.961–0.999)	0.037
Total cholesterol (continuous)	0.994 (0.988–0.999)	0.027	0.996 (0.989–1.004)	0.322
PSA (continuous)	1.098 (0.986–1.222)	0.089		
Serum testosterone (continuous)	0.928 (0.829–1.039)	0.194		
Serum albumin (continuous)	0.500 (0.262–0.954)	0.036	1.286 (0.566–2.922)	0.548
HbA1c (continuous)	1.976 (1.356–2.881)	<0.001	1.889 (1.259–2.835)	0.002
Serum 25(OH)D level (continuous)	1.001 (0.979–1.023)	0.946		
Serum 25(OH)D level (deficiency vs. no deficiency)	1.004 (0.658–1.532)	0.984		
Q _{max} (continuous)	0.966 (0.938–0.995)	0.023	1.045 (0.995–1.096)	0.076
Voided volume (continuous)	0.998 (0.996–0.999)	0.001	0.998 (0.997–1.000)	0.051
PVR (continuous)	1.004 (0.997–1.012)	0.278		
Voiding efficiency (continuous)	0.202 (0.040–1.031)	0.054		
Prostate volume (continuous)	0.996 (0.976–1.016)	0.696		

ED: erectile dysfunction, OR: odds ratio, CI: confidence interval, IPSS: International Prostate Symptom Score, LUTS: lower urinary tract symptoms, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, eGFR: estimated glomerular filtration rate, PSA: prostate-specific antigen, HbA1c: hemoglobin A1c, 25(OH)D: 25-hydroxyvitamin D, Q_{max}: maximal urinary flow rate, PVR: post-voided residual.

Table 4. Logistic regression analyses for moderate to severe ED in the elderly men (over 60 years) complaining moderate to severe LUTS (n=223)

Variable	Univariate analysis		Multivariate analysis (I) including serum 25(OH)D level as continuous variable		Multivariate analysis (II) including serum 25(OH)D level as categorical variable	
	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Body mass index (continuous)	1.016 (0.908-1.137)	n.s	0.949 (0.756-1.192)	n.s	0.996 (0.785-1.264)	n.s
Hypertension (yes vs. no)	1.720 (0.774-3.820)	n.s	2.803 (1.016-7.729)	0.046	1.731 (0.539-5.563)	n.s
Diabetes mellitus (yes vs. no)	2.609 (0.733-9.280)	n.s	1.627 (0.131-20.144)	n.s	1.699 (0.140-20.608)	n.s
Dyslipidemia (yes vs. no)	0.995 (0.197-5.037)	n.s	0.558 (0.040-7.871)	n.s	0.600 (0.039-9.297)	n.s
Serum hemoglobin (continuous)	0.863 (0.641-1.160)	n.s	0.856 (0.537-1.362)	n.s	0.835 (0.523-1.334)	n.s
ESR (continuous)	0.993 (0.959-1.028)	n.s	0.975 (0.912-1.042)	n.s	0.967 (0.906-1.032)	n.s
CRP (continuous)	1.472 (0.753-2.876)	n.s	1.459 (0.562-3.788)	n.s	1.376 (0.565-3.351)	n.s
Serum creatinine (continuous)	0.940 (0.774-1.142)	n.s	1.438 (0.000-23,107.711)	n.s	0.344 (0.000-3,367.769)	n.s
eGFR (continuous)	0.977 (0.946-1.009)	n.s	0.975 (0.867-1.096)	n.s	0.969 (0.865-1.086)	n.s
Total cholesterol (continuous)	0.992 (0.980-1.005)	n.s	0.993 (0.975-1.011)	n.s	0.993 (0.975-1.010)	n.s
PSA (continuous)	1.119 (0.921-1.358)	n.s	1.061 (0.796-1.415)	n.s	1.058 (0.795-1.409)	n.s
Serum testosterone (continuous)	0.900 (0.722-1.121)	n.s	0.841 (0.587-1.206)	n.s	0.869 (0.613-1.233)	n.s
Serum albumin (continuous)	0.953 (0.236-3.858)	n.s	1.114 (0.099-12.525)	n.s	1.244 (0.118-13.092)	n.s
HbA1c (continuous)	1.430 (0.738-2.769)	n.s	1.540 (0.489-4.849)	n.s	1.530 (0.499-4.692)	n.s
Serum 25(OH)D level (continuous)	0.952 (0.915-0.992)	0.019	0.944 (0.903-0.986)	0.010		
Serum 25(OH)D level (deficiency vs. no deficiency)	2.915 (1.235-6.878)	0.015			2.949 (1.118-7.782)	0.029
Qmax (continuous)	1.001 (0.934-1.071)	n.s	1.094 (0.944-1.267)	n.s	1.097 (0.948-1.269)	n.s
Voided volume (continuous)	0.998 (0.995-1.001)	n.s	0.996 (0.989-1.002)	n.s	0.995 (0.988-1.001)	n.s
PVR (continuous)	1.014 (0.996-1.032)	n.s	1.012 (0.981-1.045)	n.s	1.015 (0.984-1.047)	n.s
Voiding efficiency (continuous)	0.049 (0.002-1.373)	n.s	0.846 (0.001-828.922)	n.s	2.706 (0.003-2,217.312)	n.s
Prostate volume (continuous)	0.988 (0.958-1.019)	n.s	0.965 (0.921-1.011)	n.s	0.964 (0.920-1.009)	n.s

ED: erectile dysfunction, LUTS: lower urinary tract symptoms, OR: odds ratio, CI: confidence interval, 25(OH)D: 25-hydroxyvitamin D, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, eGFR: estimated glomerular filtration rate, PSA: prostate-specific antigen, HbA1c: hemoglobin A1c, Qmax: maximal urinary flow rate, PVR: post-voided residual.

the presence of vitamin D deficiency were not (Table 3).

Based on the results of this analysis, a subgroup (n=223) consisting of moderate to severe LUTS patients over 60 years was considered for additional analysis. To determine the significant factors related to moderate to severe ED, univariate and multivariate logistic regression analyses using two separate models, which included serum 25(OH)D level as a continuous or categorical variable was performed in the subgroup (Table 4). The results revealed that either decreasing serum 25(OH)D level (OR, 0.944; 95% CI, 0.903–0.986) or vitamin D deficiency (OR, 2.949; 95% CI, 1.118–7.782) were the independent risk factors of moderate to severe ED in moderate to severe LUTS patients over 60 years. These significant correlations between vitamin D status and ED were not observed on the analyses performed in the other three subgroups (<60 years with mild LUTS group, <60 years with moderate to severe LUTS, and ≥60 years with mild LUTS group).

DISCUSSION

The well-known physiologic role of vitamin D is for calcium homeostasis and bone metabolism to maintain skeletal health [17]. Vitamin D ensures the maintenance of adequate concentrations of calcium and phosphate in circulation by promoting calcium and phosphate absorption in the intestine and optimizing the mineralization of the bone by providing these minerals to bone-forming sites [17,29]. Other than this skeletal action, vitamin D performs various extra-skeletal actions through the regulation of hormone secretion, cell proliferation and differentiation, and anti-inflammatory, anti-apoptotic, and anti-fibrotic effects by mediating with specific receptors for vitamin D, which are expressed in most cells and tissues throughout the human body [17,23,29]. Therefore, it has been reported that the lack of vitamin D may be associated with an increased risk of several medical health problems such as stroke, CVD, atherosclerosis, hypertension, diabetes, and some autoimmune diseases (*i.e.* rheumatoid arthritis) [15-19,29].

Notable extra-skeletal actions of vitamin D related to the development of vascular diseases is to normally maintain endothelial function by stimulating NO production that protects against oxidative stress and preventing endothelial apoptosis [13,14]. In other words, the lack of vitamin D can contribute to the development

of END. Consequently, as END is a key preceding step in the pathogenesis of ED as well as other vascular diseases, including CVD, atherosclerosis, hypertension, and diabetes [10-12], the erectile function can be affected by the vitamin D status modulating endothelial function. Recent observational studies have consistently reported the significant correlation between vitamin D deficiency and ED. In an observational study consisting of 92 type-2 diabetes patients, vitamin D deficiency (defined as 25(OH)D level of <10 ng/mL) was the independent risk factor of ED [21]. The cross-sectional study of 3,390 men aged ≥20 years without atherosclerotic CVD demonstrated that ED males showed significantly lower 25(OH)D levels than no ED males (22.8 ng/mL *vs.* 24.3 ng/mL), and vitamin D deficiency was a significant risk factor of ED prevalence, independent of lifestyle variables, comorbidities, and medication use [22]. Another study reported that compared to healthy men who had the recommended vitamin D levels within the reference range (30–80 ng/mL), the patients with vitamin D deficiency presented a high frequency of ED (40% *vs.* 6%) as well as lower scores for erectile function, orgasmic function, and sexual desire after evaluation using the IIEF-15 questionnaires [23]. Some reports have also demonstrated the association between vitamin D deficiency and LUTS severity in BPH or OAB. In an observational case-control study including 224 elderly Chinese men, the vitamin D deficiency group showed a bigger prostate volume (42 mL *vs.* 28 mL), higher PSA level (3.28 ng/mL *vs.* 2.55 ng/mL), higher IPSS scores (4.47 *vs.* 1.98), and lower Qmax (13.44 mL/s *vs.* 29.98 mL/s) than the no vitamin D deficiency group [25]. Furthermore, vitamin D levels changed significantly depending on whether patients had LUTS or not (40.82 nmoL/L in LUTS group *vs.* 70.25 nmoL/L in no LUTS group) in another case-control study [26]. Recently, it was reported that vitamin D deficiency in male LUTS patients may play a role in aggravated OAB symptoms, especially in the winter season [27]. In most of the aforementioned studies, vitamin D deficiency was defined as serum 25(OH)D levels of <20 ng/mL.

In this study, we aimed to elucidate the factors related to ED in male LUTS patients. The moderate to severe LUTS group showed advanced age, lower IIEF-5 total scores, and a higher frequency of moderate to severe ED than the mild LUTS group. Furthermore, both old age (≥60 years) and moderate to severe LUTS

were the independent risk factors of moderate to severe ED based on our multivariate analyses. Aging and LUTS severity are known to be closely related to ED as reported in previous literature [6-9], and their correlations can also be identified in this study. Although the underlying causal mechanisms between LUTS and ED have not been fully understood, the relationship between LUTS and ED may be explained by four pathophysiological mechanisms: alteration in NO bioavailability, α 1-adrenergic receptor hyperactivity, pelvic atherosclerosis, and sex hormones [6]. Also, a growing body of evidence suggests that pathophysiological mechanisms associated with metabolic syndrome may be important key factors in both disorders [6-9]. Therefore, considering this relationship, it is recommended that men presenting with LUTSs or ED should be assessed for both disorders.

On the other hand, unlike previous reports [25-27], vitamin D status, including serum 25(OH)D level and distribution of vitamin D deficiency, showed no significant difference according to LUTS severity, and there were no significant differences in urination-related parameters in this study. Besides, vitamin D status showed no significant correlation with the severity of ED and was not a significant factor related to ED based on our univariate analysis, which is inconsistent with the results of previous studies [20-23]. Therefore, we constructed and analyzed a subgroup of moderate to severe LUTS patients whose ages exceeded 60 years. Both characteristics (old age and moderate to severe LUTS) were the significant factors related to moderate to severe ED in the entire cohort. As a result of the multivariate analyses performed in this subgroup, both low serum 25(OH)D level and vitamin D deficiency were the independent risk factors of moderate to severe ED. However, these associations were not observed in the analyses performed in other subgroups based on age and LUTS severity. Our study thus suggests that low vitamin D level is associated with the occurrence of moderate to severe ED in men over 60 years with moderate to severe LUTS.

The present study has some limitations. First, we only used the IIEF-5 questionnaire to evaluate the severity of ED. Second, the imaging study such as penile echo-color-Doppler ultrasonography with erection inducer (prostaglandin E1) was not considered to assess the basal conditions of the penis. If considered, it would be possible to classify the exact type of ED

(*i.e.* arteriogenic *vs.* non-arteriogenic) and obtain more information regarding the role of vitamin D in each type of ED. Third, owing to the nature of the retrospective study, it was not possible to completely obtain information about phosphodiesterase 5 inhibitors and testosterone replacement therapy that can affect erectile status of the patients included in this study. Last, our study suggested a potential indication of vitamin D supplementation to improve erectile function in male LUTS patients. However, in real clinical practice, it is still unknown whether maintaining serum 25(OH)D at the proper level through vitamin D supplementation helps recover erectile function in male LUTS patients. To verify this hypothesis, relevant clinical trials must be conducted.

CONCLUSIONS

Vitamin D deficiency may contribute to the occurrence of moderate to severe ED in elderly males (60 years or older) with moderate to severe LUTS. Additional well-designed, prospective clinical studies are required to verify our results.

Conflict of Interest

The authors have nothing to disclose.

Author Contribution

Conceptualization: HSK, MCC. Data curation: HSK, MCC. Formal analysis: HSK. Funding acquisition: HSK, MCC. Investigation: HSK, MCC. Methodology: HSK, MCC. Project administration: HSK, MCC. Resources: HSK, MCC. Software: HSK. Supervision: MCC. Validation: HSK, MCC. Visualization: HSK, MCC. Writing – original draft: HSK. Writing – review & editing: HSK, MCC.

Data Sharing Statement

The data analyzed for this study have been deposited in HARVARD Dataverse and are available at <https://doi.org/10.7910/DVN/9S04EX>.

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