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Effects of Vitamin D Supplementation on Testosterone, Prostate, and Lower Urinary Tract Symptoms: A Prospective, Comparative Study

Jeong Kyun Yeo[1], Sun Gu Park[2,3], Min Gu Park[1]

[1]*Department of Urology, Inje University Seoul Paik Hospital, Inje University College of Medicine, Seoul,* [2]*Department of Clinical Laboratory Science, Daejeon Health Institute of Technology, Daejeon,* [3]*Department of Biomedical Laboratory Science, College of Software and Digital Healthcare Convergence, Yonsei University, Wonju, Korea*

Purpose: Several studies have associated the serum vitamin D level with total testosterone levels and the prostate volume. Herein, we investigated the effect of vitamin D supplementation on testosterone, prostate, and lower urinary tract symptoms (LUTS) in men.

Materials and Methods: Men over 40 years of age diagnosed with a vitamin D deficiency (25[OH]D <20 ng/mL) who received vitamin D supplementation for one year were included in the study and administered 25,000 IU of cholecalciferol every 2 weeks. Prostate ultrasound, uroflowmetry, postvoid residual urine volume measurement, and serological tests (serum testosterone levels, *etc*.) were performed upon diagnosis and one year later. Participants also answered the International Prostate Symptom Score (IPSS) and Aging Males' Symptoms Scale (AMS) questionnaires.

Results: A significant increase was observed in the vitamin D level following one year of vitamin D supplementation, with a significant decrease in the postvoid residual urine volume, total IPSS score and without a significant change in the prostate volume. Improved psychological subscale score of AMS questionnaire was observed with a statistical significance.

Conclusions: Vitamin D supplementation suppressed the increase in the prostate volume and improved the LUTS. Although there is no direct effect on serum testosterone levels, vitamin D supplementation helped improve hypogonadal symptoms.

Keywords: Hypogonadism; Lower urinary tract symptoms; Prostate; Testosterone; Vitamin D

INTRODUCTION

A vitamin D deficiency often occurs due to a lack of exposure to sunlight, and in severe cases, it results in the loss of bone density and osteoporosis [1,2]. A vitamin D deficiency is also associated with general weakness, inflammatory diseases, cardiovascular diseases, and higher all-cause mortality [1,3-5]. The relationship between vitamin D levels and metabolic syndrome has been reported previously, and a vitamin D deficiency is identified as a major risk factor for cancer and cardiovascular diseases, thus highlighting the importance of vitamin D supplementation in high-risk patients [6]. The clinical value of vitamin D is continuously being

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Correspondence to: Min Gu Park https://orcid.org/0000-0001-5704-5320
Department of Urology, Inje University Seoul Paik Hospital, Inje University College of Medicine, 9 Mareunnae-ro, Jung-gu, Seoul 04551, Korea.
Tel: +82-2-2270-0078, **Fax:** +82-2-2270-0226, **E-mail:** uromgpark@gmail.com

studied in urology. Several clinical studies have shown a strong correlation between a vitamin D deficiency and benign prostatic hyperplasia (BPH) and lower urinary tract symptoms (LUTS) [7,8]. The molecular mechanism involved in vitamin D signaling is widely established. By binding to the vitamin D receptor (VDR), vitamin D increases prostate cell differentiation and apoptosis and decreases cell proliferation [9]. Furthermore, vitamin D has pronounced immunoregulatory and anti-inflammatory properties and acts by regulating the growth of prostate stromal cells [10].

Meanwhile, the existence of VDR and vitamin D-metabolizing enzymes in the adult male reproductive tract, male germ cells, and Leydig cells is well known [2,11]. Several studies have reported conflicting results regarding vitamin D levels and testosterone levels or hypogonadism. Some studies have reported a significant correlation between vitamin D levels and serum testosterone levels [12,13], whereas other studies have been unable to prove it with statistical significance [14,15]. Park et al [16] suggested the possible involvement of metabolic disorders as the reason for the difference in the correlation between vitamin D and serum testosterone levels across different studies. Therefore, the clinical value of vitamin D may vary in hypogonadism and BPH-LUTS depending on the presence or absence of metabolic syndrome [16].

The ideal method to confirm the role of vitamin D in prostate-LUTS and testosterone levels would be by assessing the changes following vitamin D supplementation. Therefore, this study aimed to determine the changes in hypogonadal symptoms, including testosterone levels, the prostate volume, and LUTS, following vitamin D supplementation in men diagnosed with a vitamin D deficiency.

MATERIALS AND METHODS

Men over 40 years of age diagnosed with a vitamin D deficiency, with a serum 25(OH)-vitamin D level of 20 ng/mL or lower, and those who agreed to receive vitamin D supplementation for one year were included in the study. Subjects were sequentially enrolled, and the following examinations were performed: prostate volume using transrectal ultrasound, uroflowmetry, postvoid residual urine volume test, testosterone level assessment, and completion of the International Prostate Symptom Score (IPSS) and Aging Males' Symptoms Scale (AMS) questionnaires. The height and weight were measured before starting vitamin D supplementation, and serological studies on prostate-specific antigen (PSA), hemoglobin, hematocrit, glucose, and total cholesterol levels were conducted. All the above parameters were re-evaluated after one year. Subjects were excluded from the study using the following exclusion criteria: those who started taking 5-alpha reductase inhibitor in the last 6 months, who started new medications for LUTS in the last 3 months, who started testosterone replacement in the last 3 months, who started taking new phosphodiesterase type 5 inhibitor in the last 3 months, with a PSA level of 3.0 ng/mL or higher, with chronic kidney disease (glomerular filtration rate <30 mL/min/m^2), and with renal stones.

Men who visited the Health Examination Center at our hospital and underwent the men's health checkup program, including prostate volume measurement, uroflowmetry, postvoid residual urine volume measurement, serum PSA level assessment, testosterone measurements, and IPSS and AMS questionnaires were considered for control subjects. Subjects with a serum 25(OH)-vitamin D level of 20 ng/mL or lower, who revisited the center for the men's health checkup program after one year, and who were similar to subjects in the experimental group were finally selected as age-matched controls.

The number of subjects in the experimental and control groups was analyzed using the G*power program [17]. The number of subjects required to maintain a power of 0.9 at the 0.05 significance level and the 0.8 effect size was 68, with 34 subjects per group. With anticipated dropouts (10%), a total of 76 subjects (38 per group) was selected *via* convenience extraction.

Men in the experimental group initially received an intramuscular injection of 200,000 IU of cholecalciferol. After 3 months, 25,000 IU of oral cholecalciferol (1 tablet) was administered every 2 weeks and was continued for 9 months.

1. Statistical analysis

The baseline characteristics of participants in both groups before the vitamin D treatment were compared using an independent t-test and chi-squared tests. The changes in the experimental group before and after treatment and changes in the control group after one year were compared and analyzed using paired t-tests. The level of significance was set at $p<0.05$. All statisti-

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cal analyses were performed using the SPSS software version 20.0 (IBM Corp., Armonk, NY, USA).

2. Ethics statement

The present study protocol was reviewed and approved by the institutional review board of Inje University Seoul Paik Hospital (Protocol No. 2018-10-012-009). Informed consent was submitted by all subjects when they were enrolled.

RESULTS

A total of 38 subjects were enrolled in the experimental group (Group 1), but 9 subjects did not complete the full year of vitamin D treatment and were lost to follow-up, resulting in 29 subjects who completed the treatment. No one withdrew from the study due to the side effects of vitamin D supplementation. The control group (Group 2) had 28 age-matched subjects.

The average ages of the control and experimental groups were 63.19 and 65.07 years, respectively, with no significant difference between the two groups. The experimental group had a higher average body weight than the control group but showed no significant difference. The body mass index (BMI) between the groups also showed no significant differences. Differences in the presence and types of comorbidities were investigated, and the results showed no statistically

Table 1. Comparison of baseline characteristics between the two groups

Variable	Group 1 (n=29)	Group 2 (n=28)	p-value[a]
Age, y	65.07±8.46	63.19±6.19	0.361
Weight, kg	74.93±8.92	69.53±10.49	0.056
BMI, kg/m^2	25.48±2.22	25.01±3.27	0.557
Prostate volume, g	27.36±4.03	28.12±4.54	0.551
PSA, ng/mL	1.12±0.76	0.97±0.75	0.351
Hemoglobin, g/dL	15.16±1.66	15.54±1.01	0.101
Hematocrit, %	43.61±4.38	45.38±3.18	0.273
Total cholesterol, mg/dL	181.38±35.83	182.07±42.20	0.710
Glucose, mg/dL	119.15±25.78	121.45±41.28	0.622
Vitamin D, ng/mL	15.54±3.17	16.24±3.28	0.432
Testosterone, ng/mL	460.33±138.34	536.20±162.48	0.073
Qmax, mL/s	16.99±8.05	18.35±6.05	0.130
Postvoid urine volume, mL	39.36±36.53	29.22±41.53	0.163
IPSS			
Total score	8.50±3.46	9.89±6.01	0.435
QoL score	2.25±1.16	2.00±1.23	0.603
AMS			
Somato-vegetative subscale	11.61±4.23	13.67±2.70	0.654
Psychological subscale	6.78±1.87	7.33±1.58	0.405
Sexual subscale	11.28±3.51	10.78±3.15	0.052
Total score	29.67±7.90	31.78±5.78	0.895
Comorbidities			0.680
Hypertension	4/27	5/26	
Diabetes Mellitus	4/27	3/26	
Dyslipidemia	5/27	3/26	
Cerebrovascular disease	2/27	1/26	
BPH-LUTS	6/27	3/26	

Values are presented as mean±standard deviation or number only.
BMI: body mass index, PSA: prostate-specific antigen, Qmax: uroflowmetry maximal flow rate, IPSS: International Prostate Symptom Score, QoL: quality of life, AMS: Aging Males' Symptoms Scale, BPH-LUTS: benign prostate hyperplasia and lower urinary tract symptoms.
Group 1: vitamin D supplement group, Group 2: controls.
[a]Independent t-test or chi-square test.

significant differences between the two groups. The mean prostate volumes for the control and experimental groups were 28.12 g and 27.36 g, respectively, and showed no significant difference. PSA showed no difference between the two groups at 0.97 and 1.12 ng/mL. Serum testosterone levels were also higher in the control group than in the experimental group, but no statistically significant difference was observed (Group 1: 460.33 ng/mL, Group 2: 536.20 ng/mL). Serum vitamin D levels showed no significant difference between the control and experimental groups at 16.24 and 15.54 ng/mL, respectively. No significant differences were shown between the two groups for Qmax (maximum urinary velocity) and the postvoid residual urine volume. The total and quality of life (QoL) IPSS scores and the subscales and total AMS questionnaire scores showed no significant difference between the groups (Table 1).

The mean prostate volume in the control group increased significantly, from the baseline test result of 28.12 g to 29.46 g when re-evaluated one year later ($p<0.001$). However, no significant changes were observed in the serum testosterone, vitamin D, Qmax, postvoid residual urine volume, and IPSS and AMS scores (Table 2).

On the other hand, the experimental group showed no significant change in the mean prostate volume between the baseline test result and after taking vitamin D supplements for one year. The vitamin D level significantly increased to 30.90 ng/mL and reached a normal range ($p<0.001$). Serum testosterone levels increased from 460.33 to 489.17 ng/dL, but the change was not statistically significant. In uroflowmetry, there was no significant change in Qmax, but the postvoid residual urine volume was significantly decreased after vitamin D treatment ($p=0.014$). The total IPSS score showed improvements in symptoms after vitamin D supplementation ($p=0.040$), and a significant symptom improvement in the psychological subscale was confirmed in the AMS score ($p=0.007$) (Table 3).

DISCUSSION

Multiple studies have failed to show a consistent as-

Table 2. Comparison between baseline and 1-year follow-up data in controls

Variable	Baseline	Post-treatment	p-value[a]
Weight, kg	69.53±10.49	69.55±10.13	0.962
BMI, kg/m^2	25.01±3.27	24.42±3.16	0.172
Prostate volume, g	28.12±4.54	29.46±4.91	<0.001
PSA, ng/mL	0.97±0.75	0.98±0.73	0.891
Hemoglobin, g/dL	15.54±1.01	15.53±0.86	0.962
Hematocrit, %	45.38±3.18	45.35±2.50	0.946
Total cholesterol, mg/dL	182.07±42.20	183.04±35.13	0.864
Glucose, mg/dL	121.45±41.28	118.52±25.97	0.358
Vitamin D, ng/mL	16.24±3.28	17.38±5.23	0.254
Testosterone, ng/mL	536.20±162.48	501.10±216.97	0.278
Qmax, mL/s	18.35±6.05	19.13±8.86	0.788
Postvoid urine volume, mL	29.22±19.53	30.41±18.41	0.500
IPSS			
Total score	9.89±6.01	9.25±4.92	0.490
QoL score	2.00±1.23	2.13±1.25	0.563
AMS			
Somato-vegetative subscale	13.67±2.70	14.00±3.07	0.962
Psychological subscale	7.33±1.58	6.75±1.49	0.442
Sexual subscale	10.78±3.15	9.50±2.56	0.461
Total score	31.78±5.78	30.25±6.04	0.511

Values are presented as mean±standard deviation.
BMI: body mass index, PSA: prostate-specific antigen, Qmax: uroflowmetry maximal flow rate, IPSS: International Prostate Symptom Score, QoL: quality of life, AMS: Aging Males' Symptoms Scale.
[a]Paired t-test.

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Table 3. Comparison between baseline and post-treatment data in vitamin D supplement group

Variable	Baseline	Post-treatment	p-value[a]
Weight, kg	74.93±8.92	74.46±10.99	0.624
BMI, kg/m^2	25.48±2.22	25.29±3.14	0.648
Prostate volume, g	27.36±4.03	27.89±3.88	0.340
PSA, ng/mL	1.12±0.76	1.25±1.06	0.332
Hemoglobin, g/dL	15.16±1.66	14.90±1.34	0.212
Hematocrit, %	43.61±4.38	44.15±3.83	0.347
Total cholesterol, mg/dL	181.38±35.83	190.04±31.56	0.693
Glucose, mg/dL	119.15±25.78	111.58±21.97	0.387
Vitamin D, ng/mL	15.54±3.17	30.90±8.39	<0.001
Testosterone, ng/mL	460.33±138.34	489.17±189.42	0.193
Qmax, mL/s	16.99±8.05	17.33±4.86	0.854
Postvoid urine volume, mL	39.36±36.53	18.41±16.41	0.014
IPSS			
Total score	8.50±3.46	7.47±3.82	0.040
QoL score	2.25±1.16	1.68±1.20	0.145
AMS			
Somato-vegetative subscale	11.61±4.23	11.23±4.25	0.927
Psychological subscale	6.78±1.87	6.01±1.75	0.007
Sexual subscale	11.28±3.51	10.24±2.93	0.128
Total score	29.67±7.90	27.65±6.74	0.128

Values are presented as mean±standard deviation.
BMI: body mass index, PSA: prostate-specific antigen, Qmax: uroflowmetry maximal flow rate, IPSS: International Prostate Symptom Score, QoL: quality of life, AMS: Aging Males' Symptoms Scale.
[a]Paired t-test.

sociation between vitamin D and testosterone [12-15]. Nonetheless, the effects of vitamin D are presumably mediated by the existence of VDR and vitamin D-metabolizing enzymes in the adult male reproductive tract, male germ cells, and Leydig cells [2,11]. Therefore, several studies have been conducted to confirm the effect of vitamin D supplementation on serum testosterone levels in patients with a vitamin D deficiency. A placebo-controlled randomized study conducted on nondiabetic overweight men for one year showed that the group that received vitamin D supplementation had significant increases in total testosterone and free testosterone levels compared with those in the placebo group [18]. More recently, a prospective single-arm study by Canguven et al [19] showed that vitamin D supplementation for one year in 50 erectile dysfunction patients with a vitamin D levels <30 ng/mL showed a significant increase in the serum total testosterone level, a decrease in BMI, an improvement in the lipid profile, a decrease in HbA1c, and an increase in erections.

In this study, testosterone levels tended to increase following vitamin D supplementation, but no statistically significant changes were observed. The weak statistical power could be due to the relatively small sample size. Moreover, our previous study showed no significant correlations between serum vitamin D, testosterone, and hypogonadal symptom scores in patients with metabolic syndrome [16]. Combined with these results, we implicate that factors related to metabolic syndrome have hindered the direct effect of vitamin D on the serum testosterone level.

A randomized control trial (RCT) conducted for three months in men with total testosterone levels >300 ng/dL and vitamin D levels <30 ng/mL, to confirm the effect of vitamin D supplementation, showed no significant change in the total testosterone but a positive change in insulin sensitivity [20]. A similar RCT in men with hypogonadism and a vitamin D deficiency (vitamin D <30 ng/mL and total testosterone <300 ng/dL) also showed no significant increase in the total testosterone following vitamin D supplementation [21]. A clinical trial with vitamin D supplementation for 6–16 weeks was not associated with any significant increase

in testosterone levels [22]. However, most of these studies had a short vitamin D supplementation period of 3–6 months, focused on changes in serum testosterone levels, and did not evaluate changes in actual hypogonadal symptoms.

The present study confirmed a significant improvement in the AMS psychological subscale score symptoms following vitamin D supplementation for a year. Even though the patients included in the study did not present significant psychological issues, the study suggests that vitamin D supplementation may help with the psychological problems accompanying the hypogonadal symptoms in men over 40 years of age. The relevance of vitamin D in physical and mental health, including depression, has been described previously [23]. However, the results of these studies remain inconsistent and debatable, with few studies describing no significant effect [24]. In addition to depression, the positive effect of vitamin D supplementation has also been associated with a reduction in the occurrence of negative emotions and an improved QoL [25]. Further understanding of the effect of vitamin D on the mental health of men would be beneficial in treating hypogonadal symptoms.

Several *in vitro* and animal studies have reported the effect of vitamin D on prostate growth and LUTS. Vitamin D analogs have a positive effect on the inhibition of cellular prostate growth and apoptosis in prostate cells [26]. It is known that vitamin D has an inhibitory effect on the Rho A/Rho-associated protein kinase (ROCK) pathway [27]. Vitamin D-mediated inhibition of the Rho A/ROCK pathway could improve the overactive bladder (OAB) symptoms by reducing the contractile tone of the bladder, and Yoo et al [28] reported that vitamin D intake reduced OAB symptoms. Total IPSS score improvements in the present study could also be attributed to this effect. BPH is a common age-related disease occurring in older men. Elocalcitol, a vitamin D3 analog, was shown to inhibit interleukin (IL)-8 production in BPH cells, reduce cyclooxygenase-2 expression and prostaglandin E2 production, and arrest NF-kB p65 nuclear translocation [29]. If the inflammatory response and cell growth in BPH stromal cells can be inhibited through vitamin D administration clinically, it can be expected to prevent prostate growth. In fact, in the present study, the prostate volume did not increase after one year of vitamin D supplementation, whereas the control group showed a significant increase in the prostate size. The improvement of the postvoid residual urine volume and total IPSS score in the experimental group is also presumed to be related to these effects of vitamin D on the prostate.

Unlike previous studies, this study has a great advantage in that it confirmed the effects of vitamin D supplementation on both prostate-LUTS and testosterone/hypogonadism simultaneously. Moreover, previous studies often only used the prostate volume, PSA level, and IPSS score to evaluate the effect of vitamin D on the prostate and LUTS; along with these, this study also used Qmax and the postvoid residual urine volume in the evaluation. Previous studies have evaluated the effects of vitamin D on hypogonadism *via* changes in total testosterone levels. The present study evaluated changes in hypogonadal symptoms using the AMS questionnaire. Furthermore, while most vitamin D supplementation studies conducted evaluations after a treatment period as short as 3 months to as long as 6 months, this study conducted vitamin D supplementation for one year. It has already been reported that seasonal differences in sunlight can affect vitamin D levels [28,30]. This study obtained data from only the age-matched control group who underwent health checkups at one-year intervals to minimize the effect of seasonal differences.

Despite the efforts of the authors, this study had several limitations. First, the study did not include a placebo-controlled randomized design. Since it would have been difficult to conduct a placebo-controlled study for one year, a comparative study was conducted by constructing a control group with age-matched vitamin D-deficient subjects among those who used the men's health checkup program at the same time every year. Furthermore, this study intended to investigate the effect of vitamin D supplementation on serum testosterone levels, hypogonadal symptoms, prostate conditions, and LUTS; however, since the overall number of participants was small, it was not possible to separately analyze the data of patients with BPH who complained of LUTS with an IPSS score of 8 or higher and patients with hypogonadism with a total testosterone level of 350 ng/mL or lower. Another limitation was that the effect of the metabolic component of vitamin D could not be evaluated as HbA1c, which can confirm insulin sensitivity, and triglyceride, high-density lipoprotein, and low-density lipoprotein levels, which can evaluate dyslipidemia, were not included in

the evaluation.

Nonetheless, through this exploratory study in which vitamin D supplementation was conducted for a relatively longer period of time, we had an opportunity to evaluate the clinical value of vitamin D in the prostate, LUTS, hypogonadism, and other diseases in the urological field. To further clarify the effect of vitamin D on prostate-LUTS and testosterone levels, a large-scale, randomized, placebo-controlled study with more detailed conditions is necessary in the future.

CONCLUSIONS

In men with a vitamin D deficiency, supplementation of vitamin D suppressed the increase in the prostate volume. Improvements were noted in LUTS, such as a reduced postvoid residual urine volume and symptom questionnaire scores. Although there is no direct effect on serum testosterone levels, vitamin D supplementation helped improve hypogonadal symptoms.

Conflict of Interest

The authors have nothing to disclose.

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Author Contribution

Conceptualization: MGP, JKY. Formal analysis: SGP. Investigation: JKY, MGP. Methodology: SGP, JKY. Writing – original draft: JKY. Writing – review & editing: MGP, SGP.

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/NAL4HW.

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