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Original Article

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Effect of Supplemental Vitamin D on Prostate Volume in Patients with Symptomatic Benign Enlargement of Prostate

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Abstracts

Background: *Vitamin D is essential for the normal function of multiple organs of the body. Studies have suggested there is an association between vitamin D deficiency and benign enlargement of prostate (BEP).*

Objective: *To evaluate the effect of oral vitamin D supplementation on prostate volume in patients with lower urinary tract symptoms (LUTS) due to BEP.*

Methods: *This was a quasi-experimental study conducted from November 2020 to February 2022 in Urology OPD, Bangabandhu Sheikh Mujib Medical University, Dhaka. After evaluation of 132 patients, 15 were excluded for not meeting the criteria. Total 117 patients were enrolled in this study but with a drop out of 8 patients finally 109 male patients having LUTS due to BEP were purposively selected for the study. Patients received treatment with testosterone, 5-alpha-reductase inhibitors, or any other hormone therapy (in previous 6 months), having prostate or bladder cancer or Serum PSA values of >4 ng/ml were excluded from the study. Face-to-face interview and medical record review were used as the techniques for data collection. Data were collected in an interviewer administered questionnaire. A check list was also used containing International Prostate Symptom Score (IPSS) and investigation reports for collecting data regarding LUTS, prostate volume, serum vitamin D level, serum creatinine, serum PSA and urinary flow rate. After initial assessment patients with vitamin D insufficiency or deficiency were prescribed alpha-1 blocker (Tamsulosin) and oral supplementation tablet containing calcium 600mg with Vitamin D 400IU twice daily for 12 weeks. In the follow up visit after 12 weeks, IPSS score, Prostate volume, Serum 25(OH) D level of the patients were assessed again. Then the effect of the supplementation was evaluated.*

Results: *The mean (±SD) age of the patients was 61.9 ±5.7 years. Before oral vitamin D supplementation, 48 (44.0%) had deficient while 61 (66.0%) had insufficient serum 25(OH) D. The mean prostate volume of the patients was significantly lowered after oral vitamin D supplementation (29.0 ±3.2 mL) compared to before supplementation (33.8 ±3.4 mL) ($p<0.001$). The median IPSS of the patients was also significantly lowered after oral vitamin D supplementation (10.0) compared to before supplementation (14.0) ($p<0.001$). Before oral vitamin D supplementation, only 10 (9.2%) were mildly*

Keywords: Oral vitamin D supplementation, prostate volume, lower urinary tract symptoms (LUTS), BEP

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symptomatic and 99 (90.8%) were moderately symptomatic while after oral vitamin D supplementation, 28 (25.7%) were mildly symptomatic while 81 (74.3%) were moderately symptomatic (p=0.002). No significant statistical difference was observed between the patients with or without comorbidities regarding prostate volume before and after oral vitamin D supplementation (p>0.05). Prostate volume significantly reduced in normal, overweight, and obese patients after oral vitamin D supplementation (p<0.001).

Conclusion: *Oral vitamin D supplementation significantly reduced prostate volume symptom status, co-morbidity, and BMI in patients with lower urinary tract symptoms due to BEP.*

Introduction:

Benign enlargement of prostate (BEP) is characterized by over proliferation of the stromal and glandular elements of the prostate[1,2]. With increasing incidence after the age of 50 years, it has become most common debilitating condition among male population[3]. Fifty percent of men over the age of 50 will have benign enlargement of prostate[4]. At the age of 70 years the incidence of the disease is about 70% which becomes nearly universal with advancing age[3]. Benign enlargement of prostate limits the quality of life (QoL) of patients by causing bothersome lower urinary tract symptoms (LUTS)[3]. LUTS are associated with obstructive/voiding symptoms characterized by weak stream, hesitancy, intermittency and terminal dribbling and irritative/storage/filling symptoms characterized by frequency, urgency, nocturia, urgency incontinence and possibly dysuria[3]. Vitamin D, the active form of which molecularly known as 1,25-dihydroxyvitamin D3, has recently been gaining exposure in science for its impact on disease states. Epidemiological studies have suggested the association between vitamin D deficiency and benign enlargement of prostate[4]. In a cohort study, it was found that 52% of the urological patients were deficient (less than 20 ng/mL) in vitamin D[5]. It was reported that patients with vitamin D deficiency had a significantly higher prostate volume (42 mL vs 28 mL, $P < .001$) and IPSS (4.47 vs 1.98, $P < .001$), and a significantly lower maximum urinary flow (13.44 mL/s vs 29.98 mL/s, $P < .001$) compared to free of vitamin D deficiency participants[6]. Vitamin D receptors (VDR) are known to exist in prostate and bladder tissue, and agonists for the vitamin D receptor may have anti-inflammatory and antiproliferative properties[7]. In addition to the presence of the vitamin D receptor, prostatic cells can hydroxylate 25-hydroxyvitamin D (primary circulating form) to 1, 25-dihydroxyvitamin D3 (active form of vitamin D)[8]. Growth inhibitory effect of vitamin D is mediated by binding of its active form to high affinity receptor protein, the 1,25-dihydroxyvitamin D3 receptor which is also known as VDR[9]. Thus, prostate is involved in both the endocrine and autocrine pathways of vitamin D metabolism[7]. Study showed, consumption of >11µg/day (440 IU) was correlated with decreased risk of developing symptomatic benign enlargement of prostate[10]. Several studies were conducted to find out the association between prostate volume and vitamin D but only two studies observed the effect of vitamin D on prostate volume[11,12]. Moreover, no study has been found evaluating the effect of supplemental vitamin D on prostate volume in patients with symptomatic BEP among Bangladeshi population. As prostatic epithelial and stromal cells are the target of vitamin D for inhibiting the prostatic growth[13], this study has been designed to evaluate the effect of oral vitamin D supplementation on prostate volume in patients with symptomatic BEP.

Materials and Methods:

This was a quasi-experimental study conducted from November 2020 to February 2022 in the Urology OPD, Bangabandhu Sheikh Mujib Medical University, Dhaka. Male patients having LUTS) due to BEP attending at Urology OPD in BSMMU were the study population.

Inclusion criteria was Patients aged from 50 to 70 years, Benign enlargement of prostate with mild to moderate IPSS score, Prostate volume >24 to <40 ml, Patients who had vitamin D level <30 ng/mL, Patients who received á-1 blocker and oral vitamin D, Patients who gave informed written consent.

Exclusion criteria was patients treated with testosterone, 5-alpha-reductase inhibitors, or any other hormone therapy (in previous 6 months), Clinically significant bladder outlet obstruction and/or a post

void residual volume (measured by pelvic ultrasound) greater than 100 cc, history of acute urinary retention or refractory retention due to BEP within 3 months before study, Serum PSA values of >4 ng/ml, Prostate or bladder cancer**.**

Sample size was 132 out of which 15 patients were excluded for not meeting the criteria. Total 117 patients were enrolled in this study but with a drop out of 8 patients finally 109 male patients having LUTS due to BEP were purposively selected for the study. Data were collected by face-to-face interview and medical record review and IPSS questionnaire, a self-rated questionnaire with scoring from 0-35 (0-7= mild, 8-19= moderate, 20-35= severe). In this study, Bengali translated version of IPSS was used[14]. Initial assessment of patient included history taking, general, physical, and genital examination, DRE, abdominal/pelvic ultrasonography, Uroflowmetry, Serum PSA, Serum creatinine, Urine R/M/E with C/S and Serum 25(OH)D to rule out exclusion criteria. In the first visit, IPSS score was calculated, Prostate volume was measured by abdominal/pelvic USG and the patient's initial Serum 25(OH) D level was assessed. The vitamin D status was categorized as Deficiency = <20 ng/ml and Insufficiency = 20-<30 ng/ml[15]. Patients with vitamin D insufficiency or deficiency were prescribed alpha-1 blocker (Tamsulosin) and oral supplementation tablet containing calcium 600mg with Vitamin D 400IU twice daily for 12 weeks as a part of departmental treatment protocol. According to Vitamin D supplementation guideline 2018[16], recommended Vitamin D daily allowance (RDA) for age 1-70 years was 600 IU (15µg/day). In the follow up visit after 12 weeks, IPSS score, Prostate volume, Serum 25(OH) D level of the patients were assessed again. Then the effect of the supplementation was evaluated. Contact number of each patient was taken, and reminder call was given to prevent loss to follow up during the study period. The statistical analysis was conducted using SPSS (statistical package for the social science) version 26 statistical software. Associations of continuous data were assessed using paired sample t test and categorical data were assessed using McNemar's test where p<0.05 was considered significant.

Results:

Before oral vitamin D supplementation, 48 (44.0%) had deficient while 61 (66.0%) had insufficient serum 25(OH) D. The mean Serum 25(OH) D of the patients before oral vitamin D supplementation was 21.5 ±4.5 ng/mL where minimum Serum 25(OH) D was 11.8 ng/mL and maximum Serum 25(OH) D was 29.1 ng/ml (Table-I)

Table I : *Distribution of patients by Serum 25(OH) D level before oral vitamin D supplementation (n=109)*

Serum 25(OH)D	Frequency (f)	Percentage (%)
Deficient (<20 ng/mL)	48	44.0
Insufficient (20-29 ng/mL)	61	66.0
Mean±SD	21.5 ±4.5	
Minimum	11.8	
Maximum	29.1	

Table-II showed After oral vitamin D supplementation, 50 (45.9%) had insufficient vitamin D while 59 (54.1%) had sufficient serum 25(OH) D. The mean Serum 25(OH) D of the patients after oral vitamin D supplementation was 30.4 ±4.4 ng/mL where minimum Serum 25(OH) D was 22.5 ng/mL and maximum Serum 25(OH) D was 38.6 ng/ml.

Table II: *Distribution of patients by Serum 25(OH) D level after oral vitamin D supplementation (n=109)*

Serum 25(OH)D	Frequency (f)	Percentage (%)
Insufficient (20-29 ng/mL)	50	45.9
Sufficient (30-100 ng/mL)	59	54.1
Mean ±SD	30.4 ±4.4	
Minimum	22.5	
Maximum	38.6	

Before oral vitamin D supplementation, only 10 (9.2%) were mildly symptomatic and 99 (90.8%) were moderately symptomatic while after oral vitamin D supplementation, 28 (25.7%) were mildly symptomatic and 81 (74.3%) were moderately symptomatic (Fig-1). McNemar's test showed that there was significant statistical difference between the groups regarding symptoms of patients (p=0.002)

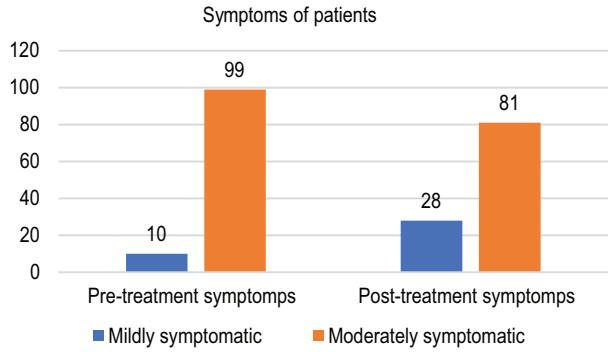

Figure-1: *Distribution of patients by symptoms according to International Prostate Symptom Score (IPSS) before and after oral vitamin D supplementation (n=109)*

The mean prostate volume of the patients before oral vitamin D supplementation was 33.8 ±3.4 ml while the mean prostate volume of the patients after oral vitamin D supplementation was 29.0 ±3.2 ml (Table-3) Paired sample t test showed that the mean prostate volume of the patients was significantly reduced after oral vitamin D supplementation (p<0.001).

Table-III: *Comparison of prostate volume before and after oral vitamin D supplementation (n=109)*

Prostate volume	Mean ±SD	p value
Before oral vitamin D supplementation	33.8 ±3.4	<0.001
After oral vitamin D supplementation	29.0 ±3.2	

*Paired sample t test

Discussion:

Vitamin D3 has been considered as an important therapeutic entity for the treatment of lower urinary tract symptoms, as it can reduce growth factor signaling aimed at cell proliferation[3]. This quasi-experimental study was conducted to evaluate the effects of oral vitamin D supplementation on prostate volume in patients with lower urinary tract symptoms due to benign enlargement of prostate. A total of 109 were treated with alpha-1 blocker (Tamsulosin) and oral supplementation tablet containing calcium 600 mg with Vitamin D 400IU twice daily for 12 weeks. After 3 months follow up, the mean prostate volume was significantly lowered compared to before supplementation.

The mean vitamin D level in this study participants was 21.5 ±4.5 ng/ml which was matched with the study of Islam, et al. (2019)[15] where the mean vitamin D level of Bangladeshi population was reported 21.66 (± 18.63) ng/ml. This is almost similar to the mean value of 21.4 ng/mL in the Indian study[17].

Before oral vitamin D supplementation, the mean prostate volume of the patients was 33.8 ±3.4 mL which significantly reduced to 29.0 ±3.2 mL after oral vitamin D supplementation (p<0.001). The study of Colli, et al. (2006)[11] also reported that vitamin D3 analog (BXL628) reduced prostate volume significantly. BXL628 reduces prostate volume via a non-antiandrogen mechanism of action. Without blocking 5-alpha reductase 1 and 2 or directly influencing the androgen receptor, it reduces cell proliferation and thereby reduces prostatic volume. Colli, et al. (2006)[11] found that Vitamin D analogues of up to 6000 IU/day have shown to decrease prostate volume in BPH patients.

Zendehdel, et al. (2021)[12] conducted a RCT to investigate the effect of vitamin D as a supplement on benign enlargement of prostate progression and reported that vitamin D significantly reduced prostate volume which is similar to the findings of this study.

In this study no significant difference was observed between the patients with or without comorbidities regarding prostate volume before and after oral vitamin D supplementation, which indicates that comorbidity does not have any significant effect on reducing prostate volume after oral vitamin D supplementation. This is also supported by Zendehdel, et al. (2021)[12] who showed that prostate volume and IPSS were significantly reduced in the intervention group regardless of co-morbidity. Moreover, in this study it was revealed that oral vitamin D supplementation had significantly reduced prostate volume in patients with any BMI range, which indicates BMI also doesn't have any significant effect on reducing prostate volume after oral vitamin D supplementation like co-morbidity. No previous study showed any relationship between BMI and reduction of prostate volume after vitamin D supplementation.

Conclusion:

In conclusion, the result of our study demonstrates that oral vitamin D supplementation significantly reduced prostate volume as well as corrects the deficiency of vitamin D irrespective of co-morbidity, BMI and symptom status in patients with LUTS due to BEP.

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