Can we link Vitamin D deficiency to benign prostatic enlargement? An observational case control study

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Introduction

Benign prostatic enlargement (BPE) is one of the most prevalent ageing-related derangements in men and has a significant impact on quality of life (1). Prevalence of BPE ranges from 40-50% at the age of 50, 80% at the age of 70 and about 90% by the ninth decade (2). It is entrenched that normal, as well as malignant prostate cells, express vitamin D receptors (3), which are responsible for regulating cell growth and replication (4,5). Vitamin D₃ and a few of its analogues can be used to modulate the growth and differentiation of prostatic cells (6). Consequently vitamin D deficiency could potentially be a modifiable risk factor for the prevention of BPE in addition to other risk factors like obesity, diabetes mellitus, diet and lifestyle (7). We aimed to study the association of prostatic volume, prostatomegaly grade and IPSS (International Prostate Symptom Score) with vitamin D deficiency if any.

Materials and methods

After obtaining approval from the Institutional Ethics Committee, an observational case-control study was conducted at Government Medical College, Calicut, Kerala, from May 2017 to December 2018. One fifty men aged between 50 to 75 years, presenting with BPE and LUTS with a negative urine dip for urinary tract infection and PSA < 4 ng/ml were enrolled in the study. The sample size was decided based on the sample size of previous studies and the fulfilment of inclusion criteria. Successively all the patients were tested for serum 25-hydroxyvitamin D 25(OH) D level. Patients diagnosed with vitamin D deficiency were classified as “cases” and those with normal vitamin D levels were classified as “controls”. All the patients had voluntarily consented to their inclusion in the study. Patients with a history of neurogenic bladder, stricture urethra, carcinoma of bladder or prostate, vesical calculi and serum PSA level > 4ng/ml were excluded from the study.

Patients with PSA of more than 4ng/ml and a family history of prostatic malignancy were referred to a cancer clinic for further evaluation.

Clinical variables

The prostate gland was assessed by digital rectal examination for size grading and the Siemens® Acuson X-300 colour Doppler machine was used for prostate volume measurement by a fixed assigned clinician. Participants were instructed to fill the International Prostate Symptom Score (IPSS) questionnaire in English/ Malayalam translation (8) which includes 7 questions, having each response scored from 0 to 5, giving a maximum score of 35. The response was graded as 0-7 being mildly symptomatic, 8-19 being moderately symptomatic, 20-35 being severely symptomatic. Prostatomegaly grading was done as per classification described by Romero et al (9). Working diagnosis of BPE was made depending on the presence of LUTS, prostate volume greater than 20 ml and serum PSA less than 4ng/ml.

Blood sampling and laboratory testing

For submitting blood samples patients were instructed to observe overnight fast and abstain from smoking for at least 12 hours. Centrifuged samples were immediately stored at -80°C before assay. The circulating form of vitamin D (25OHD) was assayed by liquid chromatography with mass spectrometry detection (LC-MS/MS). Eurolyser CUBE - S kit was utilized for measuring serum PSA levels. Vitamin D levels were classified as vitamin D deficiency (level <20ng/ml), vitamin D insufficiency (level - 20-30ng/ml) and normal level (level >30ng/ml).

Statistical analyses

Results were expressed as medians (interquartile ranges) or (mean ± standard deviation) for the quantitative variables and percentages for qualitative variables.

Qualitative variables were compared between groups using the Chi-square test. Mann-Whitney U test was done to compare the difference in the distribution of DRE grades and IPSS. Quantitative variables were compared using the T-test. Participants were divided into 2 groups, based on serum 25(OH) D levels, namely, cases (BPE with vitamin D deficiency, level <20ng/ml) and control group (BPE with vitamin D insufficiency, level 20-30ng/ml or normal level >30ng/ml).

Associations of vitamin D deficiency with prostate volume, grade and IPSS were assessed using linear regression models in multivariate adjustment, for possible confounders. The results were expressed as odds ratios (ORs) with the corresponding 95% CI. Statistical significance was defined as P value <0.05. Statistical analysis was performed using SPSS for Windows (version 24.0. Armonk, NY: IBM Corp).

Results

Participants with vitamin D deficiency (cases) were older than those with normal vitamin D levels (controls). The age difference noted was statistically significant (P=0.035). The median age of cases was 61.04 whereas the median age of controls was 57.77. The BMI (Body Mass Index) was found to be significantly higher in cases compared to the controls (P=0.029). The mean BMI in cases was 22.66 Kg/m² and in controls, it was 21.54 Kg/m².

The median serum level of 25(OH) D in the study

participants was 18.95ng/ml. Vitamin D deficiency was detected in 70% of participants, which were classified as cases and the rest 30% were classified as controls. Compared to the controls the median serum level of 25(OH) D in the cases was significantly lower 12.75 ng/ml [interquartile range, 11.22 - 15.76] vs 22.84 ng/ml [interquartile range, 21.59 - 24.04].

Prostate volume

As shown in table 1, the mean prostate volume in the cases was 41.32ml, which was 23.42ml in controls. The difference between the two was statistically significant. The prostate volume was greater than 20ml in 65.1% of cases with vitamin D deficiency versus 34.2% of controls (P<.003). There was a significant negative correlation between 25(OH) D level and prostate volume, which suggests lower the 25(OH) D levels higher the prostate volume (r = -0.328, P<.001)

Prostatomegaly grade

When the grade of prostate size was assessed by digital rectal examination (DRE) in the cases its distribution was observed as 41.9%, 35.2% and 22.9% for grades I, II and III respectively. While in the controls its distribution was 62.67% and 33.33% for grades I and II respectively. None of the controls had grade III prostatomegaly. As table 1 depicts, this difference in the distribution of prostatomegaly grades was statistically significant (P=0.001).

Table 1. Comparison for prostate volume, prostatomegaly grade, IPSS and Vit-D level between study population and controls

Parameters	Case = 105	Controls N1 = 45	P value
Prostate volume, cc (mean value $\pm$ SD)	41.32 $\pm$ 23.29	23.42 $\pm$ 8.62	<0.001*
Prostatomegaly grade	Grade I = 41.9% Grade II = 35.2% Grade III = 22.9%	Grade I = 62.67% Grade II = 33.33%	0.001*
IPSS	Mod/Severe = 78.6% Mild = 21.4 %	Mod/Severe = 21.4% Mild = 55.3%	<0.001* 0.001*
Vitamin-D Level (ng/ml) median, (interquartile range)	12.75 (11.22 - 15.76)	22.84 (21.59 - 24.04)	

Values are represented as mean value $\pm$ SD, percentages and numbers.

*significant

Table 2. Association of Vitamin D deficiency (<20 ng/ml) with prostate volume and IPSS on binary logistic regression analysis

	Odds ratio	95% confidence interval	P value
Prostate volume >20 ml	4.98	1.24 - 13.18	0.001*
Moderate to severe IPSS	4.22	2.16 - 14.76	0.001*

Values are represented as numbers

*significant

International prostate symptom score

As per table 1, for the ease of IPSS comparison, subjects were divided into two groups. Those with moderate to severe symptoms (score 9-35) and those with mild symptoms (score 0-8). The cases had significantly higher symptom scores than controls. The difference was statistically significant on the Mann Whitney U test ($P < 0.001$).

Binary logistic regression analysis showed a strong association between vitamin D deficiency in men with BPE and prostate volume greater than 20ml (OR 4.98, 95% CI 1.24 - 13.18, $P = 0.001$) as well as between the vitamin D deficiency and moderate to severe IPSS (OR 4.22, 95% CI 2.16 - 14.76; $P = 0.001$). There was no direct association noted between serum PSA level and 25(OH) D levels in cases and controls ($P > 0.05$) (Table 2).

Discussion

Although ageing and the presence of androgens are known to be the most important factors in the pathogenesis of BPE, the exact mechanism is still ambivalent. Ageing-related changes in the skin, renal function, gut absorption, and reduced sunlight exposure may adversely impact the formation of vitamin D in elderly men (10,11,12). The median age of the study population, as well as controls, was comparable with other studies (13,14). The median serum level of 25(OH) D in our participants was 18.95 ng/ml and vitamin D deficiency was detected in 70% of participants. We found that the mean prostate volume in vitamin D deficiency cases was 41.32 ml, which was significantly higher than 23.42 ml in controls. Our findings are complementary to the findings reported by Zhang et al (15). They observed that the median prostate volume in vitamin D deficiency was 42 ml and in the control group it was 28 ml. In line with our study, an inverse correlation between serum 25-OH D level <20 ng/ml and prostate volume was reported by Murphy et al (16). Our study population was found to have significantly

higher IPSS than controls. Incidence of moderate to severe IPSS was 78.6% in the study population, while it was 21.4% in controls. The difference was statistically significant. We found that vitamin D deficiency (level of <20ng/ml) is associated with moderate to severe IPSS, on binary logistic regression. The findings of our study are consistent with those of Zhang et al (15). and Mohamed Elshazly et al (13). Unlike, Elshazly et al (15). we did not find any statistically significant association between serum PSA level and 25(OH) D level.

Our study was not devoid of limitations. Enlisting a few, we did not take into consideration age-specific PSA levels, instead, we used a PSA cut off <4 ng/ml. There is a possibility of seasonal variation of Vitamin-D levels in our patients, which was not taken into consideration. The median age and BMI of cases and controls were not comparable, acting as confounding factors.

To conclude, this study was aimed to demonstrate the relationship of vitamin D deficiency with prostate volume and severity of IPSS in men with BPE. The men having BPE and vitamin D deficiency were found to have a greater prostate volume, higher prostatic atrophy grade on DRE and higher IPSS in comparison to men with BPE and normal vitamin D levels. If further studies confirm this association, vitamin D deficiency may be used as a therapeutic target for preventing and treating BPE.

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