SYSTEMATIC REVIEW

Exploring the Association Between Low Serum Vitamin D Levels and Benign Prostatic Hyperplasia: A Systematic Review

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ABSTRACT

Introduction: Benign prostatic hyperplasia (BPH) is a prevalent urologic concern that affects aging men. In addition to hormonal influences, inflammation serves as one of the common pathways for the proliferative growth of BPH. The objective of this article is to bridge the knowledge gap on the association between Vitamin D, renowned for its anti-inflammatory effect, and BPH. **Materials and methods:** A systematic search was conducted using PubMed and Cochrane library databases, covering the period from 2013 to 2024, following PRISMA 2020 guidelines. Keyword combinations of "Vitamin D" and "BPH" were used. Articles were filtered using inclusion and exclusion criteria and underwent bias assessment using the Newcastle-Ottawa Quality Assessment Scale (NOS). **Results:** This systematic review consists of 6 observational studies, involving more than 1500 male patients with and without BPH across six countries. All 6 studies suggest Lower serum vitamin D consistently correlates with larger prostate volumes. Vitamin D deficiency is linked to reduced urinary flow, with higher International Prostate Symptom Score (IPSS) but varying results regarding relationships Prostate-Specific Antigen (PSA). These findings suggest vitamin D has potential for BPH management, but larger and more standardized studies are needed. **Conclusion:** This review indicates a significant association between low serum vitamin D and larger prostate volumes in BPH. While findings for other BPH parameters vary, the potential role of vitamin D in modulating prostate size is evident.
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INTRODUCTION

Benign prostatic hyperplasia (BPH), characterized by the proliferation of smooth muscle and epithelial cells within the prostatic transition zone, poses a prevalent urologic concern for aging men (1). The burden of BPH among older men is substantial, with reported prevalence rates ranging from 26% to 36.6% (2,3). Beyond the bothersome lower urinary tract symptoms (LUTS), BPH is associated with various health issues, including an elevated risk of falls, depression, and a decline in overall well-being, affecting sleep, mental state, ability to perform daily tasks, and sexual health (4,5).

Despite its high prevalence, the etiopathophysiology of BPH remains incompletely understood. Hormonal influences, age-related tissue remodeling, metabolic factors, and inflammation are believed to play critical roles in prostatic hyperplasia (4). Recent studies have observed chronic sterile low-grade inflammation, also known as inflamm-aging, coexisting with BPH histologic changes in pathologic specimens, suggesting a potential role of inflammation in BPH development (4,6). Prostate stromal cells play a crucial role in initiating inflammatory responses by activating CD4+ lymphocytes. Thus, BPH can be considered as a type of symptomless inflammatory prostatitis, which can be triggered by various factors and pathways (7). Vitamin D, well known for its anti-inflammatory properties, has emerged as an intriguing candidate in the regulation of cell proliferation for BPH (7).Growing evidence suggests an association between vitamin D deficiency and the development of BPH (8). Furthermore, vitamin D's role as an adjuvant therapy for patients with BPH suggest its potential in mitigating prostatic hyperplasia (9).

This systematic review aims to bridge the existing knowledge gap between the potential role of vitamin D in mitigating the development and progression of BPH.

MATERIALS AND METHODS

This systematic review followed the Preferred reporting items for systematic reviews and meta-analyses (PRISMA) 2020 guidelines to examine the association between low serum vitamin D levels and benign prostatic hyperplasia (BPH).

Eligibility Criteria
Cross-sectional, cohort, case-control, and in vitro studies that evaluate the association between serum vitamin D level and benign prostatic hyperplasia were included. Studies were excluded if any of the following attributes were found: (1) Review articles and case reports; (2) Studies focusing on prostate cancer.

Information Sources
A comprehensive literature search has been conducted on two databases: Cochrane and PubMed. A Snowball search from Google Search Engine, Google Scholar, and studies cited in similar systematic review was also done to identify unindexed studies from the two databases.

Search Strategy
The investigation covered all published studies between January 2012 and June 2024, written in English. The search strategies included a combination of keywords Benign Prostate Hyperplasia and Vitamin D. Detailed search strategy can be found in the supplemented material. All retrieved records were saved in Google Sheets, extracted for title, abstract, date of publication, methodology, main results, and link for the article.

Selection Process
Four reviewers independently screened titles and abstracts of the search results based on predefined eligibility criteria. Any ambiguous studies were openly discussed among the reviewers in the subsequent selection stage. Following this, full texts of potentially relevant studies were assessed, and ineligible studies were excluded. The inclusion of studies was confirmed through consensus among all reviewers to ensure consistency.

Data Collection Process
Data extraction and analysis were recorded in Google Sheets. Four reviewers independently extracted the relevant data and cross checked their findings, actively resolving any discrepancies through discussions.

Data Items
Outcome that was extracted include characteristic of study participant, study method, serum vitamin D level (measured in ng/mL), prostate size (measured by ultrasound in ml), International Prostate Symptom Score (IPSS), Prostate-Specific Antigen (PSA) measured in ng/mL), and maximum urinary flow rate (mL/s) provided from the studies.

Risk of Bias Assessment
The quality of the included studies was assessed using the Newcastle Ottawa Scale (NOS). The NOS evaluates studies based on three domains: selection, comparability, and outcome assessment with scale scoring system. Studies scoring 7 to 9, 4 to 6, and 0 to 3 categorized as high, moderate, and low quality respectively. Each study was independently evaluated by two different reviewers, and their assessments were compared to ensure consistency. Any discrepancies were resolved through discussions involving a third and fourth reviewer.

Synthesis Methods
The findings of the study were presented through tabulation and visual representations of the methods used. A narrative synthesis was conducted to provide a comprehensive overview of the association between low serum vitamin D and BPH, as well as the factors that contribute to its development. Group discussions were routinely held by all authors to determine the correlation of results between studies.

RESULTS

Study Characteristics
A PRISMA flow diagram, presented in Figure 1, illustrates 181 potential articles matched the search terms in Cochrane and PubMed. Of these, 159 were excluded due to invalid year, irrelevant abstract or title and being unretrievable. A total of 22 studies were deemed eligible, but after reading the full text only 6 studies were included in this review. Each of these studies was subsequently evaluated using NOS. In total, the 6 selected articles encompassed data from over 1500 patients across 6 different countries. All these studies were observational, comprising 2 case-control studies and 4 cross-sectional studies. The baseline characteristics of these articles are summarized in Table I.

Table I: Characteristics of the Included Studies

Author and Year	Study Design	Country	Age Range	Sample size	Vitamin D assessment	Vitamin D threshold	Main Parameter Recorded	Main Findings
Chen et al, 2021	Cross sectional	China	58-79 Years Old	103 Vitamin D deficiency 57 Control	25-OH-Vitamin D	Vitamin D deficiency <20 ng/mL	Serum 25-OH D, Prostate Volume, Maximum Flow,IPSS, Serum PSA	Vitamin D level is decreased in patients with BPH and showed significant association with higher prostate volume, lower Qmax, higher IPSS, higher serum PSA (p<0,001).
Park et al, 2017	Cross Sectional	Korea	40-56 Years Old	477 without Metabolic Syndrome 135 with Metabolic syndrome	Vitamin D serum	NA	Serum Vitamin D, Prostate volume, IPSS, IPSS QoL	Among patients with metabolic syndrome, notably lower levels of Vitamin D were observed, although these levels did not display any correlation with prostate volume or IPSS. Conversely, in subjects without metabolic syndrome, Vitamin D exhibited a negative correlation (p=0.029) with both prostate volume and quality-of-life IPSS (p=0.033).
Elshazly et al, 2016	Case Control	Egypt	46-73 Years Old	70 with LUTS 80 Control	Vitamin D serum	Vitamin D deficiency <50 nmol/L Normal Vitamin D ≥50nmol/L	Serum Vitamin D, Prostate Size, PSA, IPSS, Maximum flow	Disparity in Vitamin D levels was evident between individuals with Lower Urinary Tract Symptoms (LUTS) and the control group (p<0.001). Similarly, there was a substantial distinction in the mean prostate size between those with LUTS and the control group (p<0.001). Moreover, the LUTS group displayed a significant difference in PSA value, Qmax uroflowmetry, and IPSS (p<0.001).
Zhang et al, 2016	Case Control	China	63-72 Years Old	231 Vit D Deficiency 91 Control	25-OH-Vitamin D	Vitamin D deficiency <20 ng/mL Vitamin D insufficiency 20 - 30 ng/mL	Serum 25(OH) Vitamin D, Prostate Volume, Maximum Flow, IPSS, PSA	The Vitamin D deficiency group had a significantly higher prostate volume (p<0.001) and prostate-specific antigen value (p<0.001), and IPSS (p <0.001) and a significantly lower maximum urinary flow (p <0.001) versus the free of vitamin D deficiency group. Binary logistic regression analysis showed a strong association between the presence of vitamin D deficiency and BPH
Caretta et al, 2015	Cross Sectional	Italy	49-67 Years Old	67 with T2DM	25-OH-Vitamin D	Normal Vitamin D >50 nM Vitamin D insufficiency >25 nM <50 nM Vitamin D deficiency <25 nM	Serum 25(OH) Vitamin D, IPSS, Prostate Volume, PSA,	Three groups of patient categorized by 25-OH-vitamin D concentration (sufficiency ≥50; insufficiency >25 < 50; and deficiency ≤25 nM), showed a significant progressive increase in prostate volume (p = 0.037) and IPSS score (p = 0.019). 25-OH-Vitamin D levels were inversely correlated with both IPSS (p = 0.006) and prostate volume (p = 0.011). At multivariate analysis, hypovitaminosis D remained an independent predictor of both IPSS and prostate volume.
Haghsheno et al, 2013	Cross Sectional	Sweden	70-75 Years old	155 osteoporotic men	25-OH-Vitamin D	NA	Serum 25-OH Vitamin D, Prostate Volume	25-OH vitamin D remains to be have strong association with large prostate glands after multivariate model analysis (p=0.024)

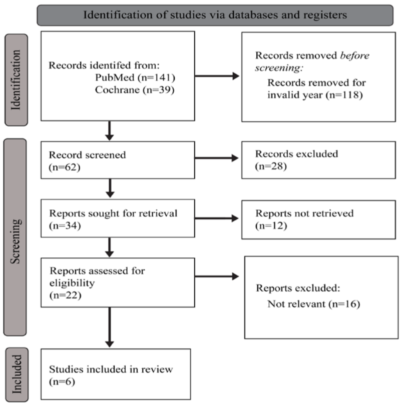

Figure 1: PRISMA 2020 flow diagram of study selection

Risk of bias assessment

Out of the 6 studies included, 2 studies were assessed as high-quality according to NOS for case-control studies, and 4 studies received high-quality ratings based on the modified NOS criteria for cross-sectional studies as shown in Table II. The primary limitation observed across these studies is the relatively small sample size, which is further compounded by the limited ethnic diversity in the study populations.

Prostate Volume

In total, six articles investigate the relationship between serum vitamin D levels and prostate volumes. All the studies showed result of higher prostate volumes accompanied by lower vitamin D levels.

Table II: Risk of Bias Assessment using Newcastle-Ottawa Scale (NOS) and Modified NOS

Study (case control)	Selection (Maximum 4 stars)				Comparability (Maximum 2 stars)	Outcome (Maximum 3 stars)			Total
	Is the case definition adequate?	Representativeness of the cases	Selection of controls	Definition of controls	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-Response rate	
Elshazly et al, 2016	*	-	*	*	**	*	*	-	7/9
Zhang et al, 2016	*	*	*	*	**	*	*	-	8/9
Study (cross sectional)	**Selection (Maximum 5 stars)**				**Comparability (Maximum 2 stars)**	**Outcome (Maximum 3 stars)**			**Total**
	Representativeness of the sample	**Sample size**	**Non-respondents**	**Ascertainment of the exposure**	**The subjects in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled.**	**Assessment of the outcome**	**Statistical test**		
Chen et al, 2021	*	*	-	*	**	**	*		8/10
Park et al, 2017	*	-	-	**	**	**	*		8/10
Caretta et al, 2015	*	-	-	**	**	**	*		8/10
Haghsheno et al, 2013	*	-	-	**	**	**	*		8/10

Zhang et al. (10) reported that among 231 Chinese elderly men with vitamin D deficiency, the prostatic volume was significantly higher (42 mL) compared to the control group (28 mL). This finding was accompanied by a negative correlation between vitamin D levels and prostatic volume ($r = -0.399$, $p < 0.001$), suggesting that lower vitamin D serum levels correlates to larger prostatic volumes. Binary logistic regression analysis, adjusted for age, aldosterone, C Reactive Protein (CRP), glucose, insulin, urinary volume, urination time, and IPSS, further confirmed a strong association between vitamin D deficiency and prostates larger than 30 mL (OR 10.12, 95% CI 2.23-25.32; $P = 0.002$). However, it is important to note that in this study the Vitamin D deficiency group displayed a higher prevalence of type 2 diabetes and a family history of BPH which might have influenced the results.

Hagsheno et al. (11) revealed a significant difference in prostate volume of 55 mL and 45 mL between patients with type 2 diabetes and healthy individuals (p= 0.036) respectively. To mitigate the influence of type 2 diabetes as a confounding factor, a univariate analysis was performed, excluding diabetes patients. This analysis indicated that 25-OH vitamin D showed a negative correlation with prostate volume (OR 1.64, p = 0.041). Subsequent stepwise exclusion of nonsignificant predictors reinforced the strong association of 25-OH vitamin D with prostate volume, alongside High-density lipoprotein (HDL) cholesterol, Sex hormone binding globulin (SHBG), and albumin-corrected serum levels (p < 0.05).

In a cross-sectional study by Caretta et al. (12), a significant negative linear correlation was found between prostate volume and 25-OH vitamin D (r = -0.311, p = 0.011), and remained significant after correction for age, Body Mass Index (BMI), systolic blood pressure, testosterone levels, and PSA among all 67 patients with type 2 diabetes. Furthermore, prostate volume differed significantly across three group levels of 25-OH vitamin D (p = 0.037). Specifically, with 50 nmol of vitamin D, prostate volume was 31.0 ± 10.3 mL, compared to 39.6 ± 13.9 mL with 25 nmol of vitamin D.

Chen et al. (8) and Elshazly et al. (13) also examined the relationship between vitamin D levels and prostate volume, both revealing significant differences. Chen et al. (8) observed 160 BPH patients where a larger prostate volume (46.5 (32.6-57.3) ml vs 31.4 (23.6-37.3) ml with p<0.001) in the vitamin D deficiency (<20 ng/mL) group compared to insufficiency or normal group. Furthermore, serum vitamin D levels differed significantly between healthy individuals and BPH patients (35.28 ng/mL vs. 16.73 ng/mL, P <0.001). Similarly, Elshazly et al. (13) demonstrated significant differences in prostate volume (50.12 grams ± 23.24 vs. 30.68 grams ± 4.90) and vitamin D levels (40.82 ± 29.46 vs. 70.25 ± 22.42) between patients with LUTS and healthy individuals, respectively. However, for this study, statistical correlation analysis between serum vitamin D and prostate size yielded no significance.

Lastly, Park et al. (14) examined the impact of metabolic syndrome components on the relationship between serum vitamin D and BPH or Lower Urinary Tract Symptoms (LUTS). While no significant difference was observed in prostate volume between patients with and without metabolic syndrome, subsequent correlation analysis revealed a significant negative correlation between Vitamin D and prostate volume (r = -0.186, p = 0.029) in patients without metabolic syndrome; nonetheless, patients with metabolic syndrome did not show any significant correlation.

IPSS Score

A negative correlation of IPSS with vitamin D are found in three of the four studies that measures it. In Zhang et al.'s (10), IPSS scores are significantly higher among patients with vitamin D deficiency in comparison to the control group (4.47 and 1.98, p < 0.001). Similar to the findings above, Caretta et al. (12) discovered a significant negative linear correlation between IPSS scores and 25-OH vitamin D levels (r = -0.333, p = 0.006). This correlation remained statistically significant even after subsequent adjustments for age, BMI, PSA, and testosterone (r = -0.305, p = 0.02). To mitigate concerns of collinearity between PSA and prostate volume, this study employed two distinct models of multiple linear regression. Both models consistently identified low 25-OH vitamin D serum levels as significant predictors for LUTS. Park et al. (14) investigated the correlation between vitamin D and IPSS, yielding inconclusive findings in both patients with and without metabolic syndrome. However, in patients without metabolic syndrome, correlation analysis revealed a significant negative correlation between vitamin D levels and IPSS-quality of life (QoL) (r = -0.184, p = 0.033).

Study by Elshazly et al. (13) also suggest a negative correlation between vitamin D and IPSS scores between patients with LUTS and healthy individuals (13.4 ± 5.3 vs. 3.4 ± 2.4).

Prostate Specific Antigen

Only two of the four studies found negative correlation in the relationship between PSA levels and serum Vitamin D levels. In the study by Elshazly et al. (13), no significant difference in mean PSA values (2.24 ± 1.95 vs 2.11 ± 0.45 with p>0.05) between patients with LUTS, which had a higher vitamin D level (40.82±29.46 vs 70.25±22.42 with P<0.001), and healthy patients. Similarly, Caretta et al. (12) did not find any significant differences in PSA values across Vitamin D deficiency, insufficient, and sufficient groups. The respective PSA values are 1.6 ± 2.1, 1.3 ± 0.9, and 1.3 ± 1.0 (p=0.783) with no significant correlation observed between them as indicated by the insignificant negative correlation (r= -0.067, p=0.602) after univariate correlation analysis. Contrary to the studies above, Chen et al. (8) reported a significant difference in PSA values between patients with vitamin D deficiency and those with normal or insufficient vitamin D levels. The PSA values in this study were 3.02 (2.53 - 4.61) for deficient patients and 2.13 (1.86 - 3.36) for those with normal or insufficient levels of vitamin D (p<0.001). Zhang et al. (10) observed significant differences in PSA levels of 3.28 (2.94 - 4.49) for patients with vitamin D deficiency and 2.55 (2.02 - 3.27) for healthy patients (p<0.001).

Urinary Maximum Flow Rate

Two studies investigated and found urinary maximum flow rate (Qmax) to be lower in individuals with vitamin D deficiency. Zhang et al. (10) explored the correlation between vitamin D deficiency and urinary maximum flow rate, revealing a significantly lower Qmax between the vitamin D deficiency group and the control group (13.44 mL/s vs. 23.44 mL/s, p < 0.001). Similarly, Chen et al. (8) also reported a significant decrease in urinary maximum flow rate among individuals with vitamin D deficiency when compared to the control group (14.44 mL/s vs. 21.37 mL/s, $p < 0.001$).

DISCUSSION

The currently understood pathogenesis of benign prostatic hyperplasia essentially boils down to age related androgen pathway, chronic sterile low-grade inflammation, and metabolic factors. Combined, these factors contribute to the increase prostate volume via proliferation of epithelial and stromal cells of the prostate, also known as the static component, and detrusor muscle tone regulation or known as dynamic component (4,10,15,16).
In this review, 6 studies reported a negative correlation between vitamin D serum levels with prostate volume (8,10–14).

There is limited evidence on the role of vitamin D in the androgen pathway. Conversion of testosterone (T) to dihydrotestosterone (DHT) using 5α-Reductase enzyme contributes to the increase prostate volume as evidence during puberty, as well as effectiveness of 5-ARIs drug in reducing static component of BPH (17,18). The available evidence from observational studies indicates a positive correlation between serum vitamin D concentrations and testosterone levels. Conversely, randomized controlled trials have consistently failed to demonstrate a significant effect of vitamin D supplementation on testosterone levels, suggesting that the association observed in observational studies may be due to confounding factors or other underlying mechanisms (19–22). This might suggest that the role of Vitamin D for BPH lies elsewhere.

Outside of aging and hormonal changes, inflammation plays the biggest role in the androgen-independent pathways regarding BPH development (23). When bonded with Vitamin D receptor (VDR), vitamin D decreases inflammation by influencing innate and adaptive immunity (8,24–26). Studies suggest vitamin D's inhibitory effects lie on pathways like RhoA/ROCK, NF-κB transcription factor, promoting T-regulatory cells, downregulation of TGFβ & STAT3 transcription factor, and reducing oxidative stress (27–31). This decrease in inflammation impacts could result in the diminishing of chronic inflammation needed for BPH development resulting in a smaller prostate size (8,10–14).

The observation that a higher International Prostate Symptom Score and a lower Qmax score are associated with vitamin D deficiency, in all the study that measures this outcome, is attributed to the larger prostate size observed in the vitamin D deficient group in the respective studies. Larger prostate glands are more likely to cause obstructive symptoms and decreased urinary flow rates, which are reflected in higher IPSS scores and lower Qmax values(32,33).

We found that the relationship between PSA and vitamin D is somewhat contradictory, with 50% of the 4 studies that measure them providing conflicting results. Other observational studies and trials that measure the effect of vitamin D and PSA suggest that there are no correlation between them(34,35).

Clinical Implications and Future Research

Little is known on how to prevent BPH thus any findings that might prevent or halt the progression of BPH carry significant clinical implications. The observed correlation between lower serum vitamin D levels and exacerbated BPH suggests that vitamin D levels play a role in the development of BPH. Our findings emphasis on the importance of sufficient dietary intake of vitamin D and appropriate sun exposure for lifestyle modifications in BPH management. These insights represent a significant step toward a more holistic and effective approach to addressing BPH and improving the quality of life for affected individuals.

Limitation of Study and Future Directions

To the best of the author's knowledge, this represents the first systematic review using observational study to investigate the potential linkage between low serum vitamin D levels and BPH. This study features a relatively modest sample size and is confined to specific ethnic groups. As a result, extrapolation of our findings to other ethnicities may yield different outcomes. Additionally, among the 6 studies encompassed in our review, 4 adopt a cross-sectional design, where this design precludes the establishment of a causal relationship and fails to capture the dynamics of chronic, long-term vitamin D status. Furthermore, diverse assay methods were employed across the studies to ascertain serum vitamin D levels, potentially introducing measurement variability. Inconsistency within the criteria defining vitamin D deficiency across the studies poses a challenge in data synthesis and interpretation. Future investigations featuring larger and more diverse cohorts, longitudinal designs, standardized assay methodologies, and unified cutoff points for vitamin D deficiency are essential to provide a more comprehensive understanding of the intricate relationship between vitamin D and BPH.

CONCLUSION

This systematic review of six studies involving over 1500 patients from various countries indicates a consistent association between lower serum vitamin D levels and larger prostate volumes in BPH. Vitamin D deficiency is also associated with higher IPSS, and lower Qmax but varies regarding its relationship with PSA levels. Further research, including larger samples size and long-term vitamin D status, is needed to confirm the clinical implications of vitamin D in BPH management.

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