RESEARCH PAPER

Immunomodulatory and Anti-Proliferative Effects of Vitamin D in Benign Prostatic Hyperplasia: A Comprehensive Review

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ABSTRACT
Background
Benign prostatic hyperplasia (BPH) is the most prevalent benign neoplasm in aging men, affecting up to 90% of men over 80 years of age. Chronic inflammation and uncontrolled cellular proliferation are now recognised as central drivers of BPH pathogenesis alongside classical androgenic mechanisms. Vitamin D, a pleiotropic secosteroid hormone, exerts its biological actions through the vitamin D receptor (VDR), which is robustly expressed in both prostatic epithelial and stromal cells. The active metabolite, 1,25-dihydroxyvitamin D_3 (calcitriol), modulates immune cell activity, suppresses pro-inflammatory cytokine cascades, and inhibits cellular proliferation through multiple overlapping molecular mechanisms.
Objectives
This review consolidates evidence on the immunomodulatory and anti-proliferative roles of vitamin D in the pathogenesis and potential management of BPH, with reference to clinical, epidemiological, and molecular data sourced from PubMed (MEDLINE).
Methods
A comprehensive literature search was conducted using PubMed, including studies published from 2000 to 2024. Search terms included combinations of 'vitamin D', 'calcitriol', 'VDR', 'benign prostatic hyperplasia', 'lower urinary tract symptoms', 'inflammation', 'proliferation', and 'immunomodulation'. Original research articles, systematic reviews, meta-analyses, and randomised controlled trials were included.
Conclusions
VDR agonists including synthetic analogues such as elocalcitol demonstrate promising efficacy in inhibiting IL-8-mediated stromal proliferation, suppressing NF-κB signalling, and reducing COX-2 expression. Clinical trials confirm improvements in prostate volume and LUTS scores following supplementation. Vitamin D deserves further evaluation as a chemopreventive and adjunctive therapeutic agent in BPH.
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1. Introduction

Benign prostatic hyperplasia (BPH) is one of the most common benign neoplasms affecting the aging male population worldwide. It is characterised by the non-malignant proliferation of both stromal and epithelial cells within the transitional zone of the prostate, leading to progressive glandular enlargement that compresses the urethra and produces lower urinary tract symptoms (LUTS).BPH is found in roughly 50% of men aged 50–60 years, rising to approximately 90% in men beyond 80 years.[1] Clinically, the condition manifests as a cluster of obstructive and irritative voiding symptoms — including nocturia, polyuria, weak urinary stream, and incomplete bladder emptying — that substantially impair quality of life.

Global epidemiological data from 1990 to 2021 document a striking 115% increase in BPH incidence and an even more dramatic rise in prostate cancer incidence of over 161%, trends driven primarily by population ageing and the rising prevalence of metabolic syndrome.[2] BPH collectively imposes an enormous clinical and economic burden on urology

services. The limitations of current pharmacological treatments — principally alpha-adrenoceptor antagonists and 5-alpha-reductase inhibitors — including their partial efficacy and side effect profiles, have sustained scientific interest in novel preventive and therapeutic targets.[3]

In this context, vitamin D has attracted significant attention. Classically recognised for its role in calcium and phosphate homeostasis, vitamin D is now established as a pleiotropic steroid hormone with broad immunological and cellular functions. Its active form, 1,25-dihydroxyvitamin D_3 {$1,25(OH)_2D_3$, calcitriol}, signals through the vitamin D receptor (VDR), a nuclear transcription factor regulating hundreds of target genes involved in cell cycle control, apoptosis, immune modulation, and inflammation.[4] The VDR is robustly expressed in both normal and hyperplastic prostate tissue, identifying the prostate gland as a direct target organ of vitamin D action.[5]

Epidemiological observations suggest an inverse relationship between vitamin D status and prostate disorders. Men with vitamin D deficiency are more likely to exhibit enlarged prostate volumes, higher IPSS scores, and greater LUTS severity.[6] Systematic reviews confirm that low serum 25(OH)D is independently associated with increased risk and severity of BPH.[7] A randomised controlled trial demonstrated that high-dose vitamin D_3 supplementation over six months significantly attenuated prostate growth and reduced IPSS scores in men with BPH.[8]

This review discusses about current evidence on the immunomodulatory and anti-proliferative mechanisms of vitamin D relevant to BPH, spanning molecular biology, experimental studies, and clinical trials. The goal is to provide a structured and critical appraisal of the evidence that positions vitamin D as a potentially valuable preventive and therapeutic agent in this condition.

2. Epidemiology and Pathogenesis of BPH

2.1 Prevalence and Global Burden

BPH represents the most frequently diagnosed benign neoplasm in men globally. Estimates suggest that over 94 million men worldwide are currently affected by clinical BPH, and the age-standardised prevalence begins rising meaningfully from the fifth decade of life.[9] A systematic analysis found the global prevalence of clinical BPH to be 26.2%, with marked variation across geographic regions and racial groups.[2]

Risk factors for BPH include advancing age, androgenic stimulation, metabolic syndrome, obesity, type 2 diabetes mellitus, cardiovascular disease, and chronic inflammation. Importantly, vitamin D deficiency — itself highly prevalent in the male urological population, particularly in older, obese, and institutionalised men — has been proposed as an independent risk modifier for both BPH and LUTS.[6] Recent epidemiological analyses in Asian and European populations have confirmed that low 25(OH)D levels independently predict larger prostate volumes and higher LUTS severity scores even after adjustment for age, BMI, and androgen status.[10] [11]

2.2 Pathophysiological Mechanisms

For decades, BPH pathogenesis was understood primarily through the lens of androgenic and oestrogen-mediated signalling. Dihydrotestosterone (DHT), the intraprostatic active androgen derived from testosterone via 5-alpha-reductase, promotes stromal and epithelial cell proliferation while inhibiting programmed cell death. However, androgens alone are insufficient to explain the complex biology of BPH; chronic inflammation has emerged as an equally important pathogenic axis.[12]

Histological studies consistently demonstrate inflammatory infiltrates in virtually all BPH specimens.[13] These infiltrates are composed predominantly of chronically activated $CD4^+$ T lymphocytes (approximately 70%), alongside B lymphocytes (15%), macrophages (15%), and mast cells.[14] As BPH develops, the infiltrate shifts towards a $CD4^+$-dominated pattern, with lymphocytes sustaining permanent activation via elevated tissue concentrations of IL-15 and IFN-γ.[13] The resulting pro-inflammatory cytokine milieu drives a self-amplifying cycle of inflammation and proliferation. T lymphocytes co-cultured with BPH stromal cells drive secretion of IL-6, IL-8, IP-10, and MCP-1, stimulating further stromal cell proliferation, angiogenesis, and extracellular matrix remodelling.[15]

IL-8, acting through CXCR1 and CXCR2, promotes epithelial cell growth, and CRISPR-mediated knockout of its receptor CXCR7 reduces BPH cell proliferation by over 50% in vitro.[16] The transcription factor NF-κB coordinates this inflammatory response, amplifying cytokine production and sustaining immune cell recruitment. The RhoA/ROCK pathway additionally regulates smooth muscle tone and cellular contractility, contributing to both the static and dynamic components of bladder outlet obstruction in BPH.[17]

3. Vitamin D: Biology, Metabolism, and Prostatic Expression

3.1 Synthesis, Activation, and Circulating Forms

Vitamin D exists in two primary dietary forms: ergocalciferol (D_2) from plant sources and cholecalciferol (D_3) from animal foods ,it is also formed from 7 Dehydro cholesterol by sunlight-driven cutaneous synthesis. Cholecalciferol thus formed undergoes sequential hydroxylation: first in the liver by CYP2R1 and CYP27A1 to produce 25-

hydroxyvitamin D_3 (calcidiol), and subsequently in the kidney by CYP27B1 (1α-hydroxylase) to yield the biologically active calcitriol.[4] Serum 25(OH)D_3 is the accepted clinical marker of vitamin D status. Deficiency is defined as levels below 20 ng/mL (50 nmol/L).

Vitamin D deficiency is highly prevalent globally, with rates of 40–78% reported in elderly male populations in the US and Europe.[7] [18] Importantly, the prostate gland itself expresses CYP27B1, enabling local autocrine and paracrine conversion of 25(OH)D_3 to calcitriol — a capacity that may be particularly relevant in BPH pathophysiology.[5] Obesity and metabolic syndrome are associated with further suppression of circulating vitamin D through volumetric dilution into adipose tissue, reduced sunlight exposure, and hepatic sequestration.[19] [20]

3.2 The Vitamin D Receptor in Prostatic Tissue

The biological actions of calcitriol are mediated through the VDR, a nuclear receptor superfamily member. Upon ligand binding, VDR heterodimerises with the retinoid X receptor (RXR) and binds to vitamin D response elements (VDREs) in gene promoter regions, modulating transcription of target genes involved in proliferation, differentiation, apoptosis, and immune regulation.[4] The VDR regulates an estimated 200–2,000 target genes.

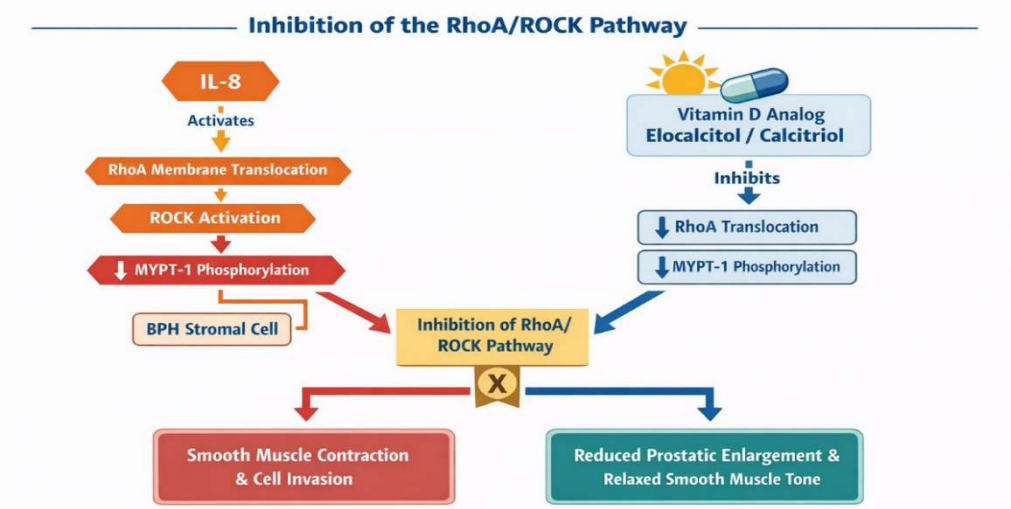
VDR expression has been confirmed in both normal and hyperplastic prostatic epithelial and stromal cells.[5] Vitamin D hydroxylases are localised particularly in stromal cells, supporting a paracrine model whereby stroma converts circulating 25(OH)D_3 and presents active calcitriol to adjacent epithelial cells.[21] VDR gene polymorphisms — including FokI (rs2228570), BsmI (rs1544410), TaqI (rs731236), and ApaI (rs7975232) — have been investigated as modulators of BPH risk, with BsmI and TaqI polymorphisms showing significant correlation ($p = 0.022$) in BPH patients.[22] These findings suggest that inter-individual variation in VDR binding affinity may influence prostatic susceptibility to calcitriol-mediated protection.

4. Anti-Inflammatory Mechanisms of Vitamin D in BPH

4.1 Suppression of NF-κB Signalling

NF-κB is a master regulator of inflammation that drives transcription of pro-inflammatory cytokines, chemokines, adhesion molecules, and COX-2. In BPH, NF-κB is constitutively activated in stromal cells, sustaining the pro-inflammatory microenvironment. Elocalcitol, a synthetic VDR agonist, potently inhibits IL-8-induced BPH stromal cell proliferation and suppresses NF-κB p65 nuclear translocation, with downstream reductions in COX-2 expression and PGE_2 production.[23] COX-2-derived PGE_2 promotes stromal fibroblast proliferation and modulates local immunity. By interrupting NF-κB at a proximal level, calcitriol simultaneously silences multiple pro-inflammatory effectors.

VDR agonists also suppress TNF-α, IL-1β, and IL-17 production, cytokines that drive paracrine crosstalk between infiltrating immune cells and prostate stromal cells, sustaining the chronic proliferative stimulus of BPH.[24] These findings have been replicated in multiple in vitro and animal model systems using both calcitriol and low-calcaemic synthetic analogues.[23] [25]



4.2 Inhibition of the RhoA/ROCK Pathway

IL-8 activates the RhoA/ROCK pathway in BPH stromal cells, promoting RhoA membrane translocation and MYPT-1 phosphorylation, thereby increasing smooth muscle tone, cellular contractility,

and invasiveness. Elocalcitol significantly inhibits both IL-8-induced RhoA membrane translocation and MYPT-1 phosphorylation.[23] This provides a mechanistic basis for anti-contractile benefits beyond anti-inflammatory actions, suggesting that VDR agonists may address both static (prostatic volume) and dynamic (smooth muscle hypertonia) components of bladder outlet obstruction.[17] Inhibition of the RhoA/ROCK pathway by VDR agonists has also been demonstrated in bladder smooth muscle, potentially extending therapeutic benefits to detrusor overactivity and overactive bladder.[26]

4.3 Immunomodulation of T Lymphocytes and Macrophages

VDR is expressed by dendritic cells, macrophages, activated T and B lymphocytes, and calcitriol binding shifts immune phenotype towards tolerance. In BPH, calcitriol suppresses $CD4^+$ T helper cell differentiation towards Th1 and Th17 phenotypes, the dominant pro-inflammatory subsets in hyperplastic prostatic tissue.[14] Th1 cells produce IFN-γ and IL-2, promoting stromal fibroblast proliferation; Th17 cells produce IL-17, synergising with IFN-γ to amplify IL-6, IL-8, and TNF-α in BPH cells. By inhibiting these subsets while promoting immunosuppressive regulatory T cells (Tregs), calcitriol attenuates these inflammatory axes at their source.[27]

Macrophage polarisation is another target of vitamin D action. In BPH, infiltrating macrophages adopt a pro-inflammatory M1 phenotype, releasing ROS, IL-1β, IL-6, and TNF-α. Calcitriol shifts macrophage polarisation towards anti-inflammatory M2, characterised by reduced pro-inflammatory cytokine secretion and increased IL-10 production.[28] [29] This shift could meaningfully reduce the intensity of the pro-inflammatory prostatic microenvironment.

4.4 Suppression of TGF-β and Growth Factor Signalling

TGF-β promotes stromal fibroblast proliferation and fibrosis, contributing to the stromal remodelling of advanced BPH, while also upregulating CYP24A1-the vitamin D-degrading enzyme, thus reducing local calcitriol bioavailability. Calcitriol attenuates TGF-β-mediated Smad-dependent signalling in prostate stromal cells, reducing fibroblast activation and extracellular matrix deposition.[30] Additionally, calcitriol modulates IGF activity, reducing BPH cell proliferation stimulated by Des(1-3)IGF-1.[7] KGF (keratinocyte growth factor) signalling, another important proliferative driver in BPH, is also inhibited by calcitriol analogues like BXL353, which reduces KGF-induced cell proliferation and induces apoptosis in BPH tissue.[31]

5. Anti-Proliferative Effects of Vitamin D in BPH

5.1 Cell Cycle Arrest

Calcitriol induces G0/G1 cell cycle arrest in prostate cells by transcriptionally upregulating the CDK inhibitors p21^(WAF1/CIP1) and p27^(KIP1), which inhibit CDK4/6-cyclin D complexes and prevent pRb phosphorylation, blocking the G1-to-S transition.[32] This mechanism has been demonstrated in both normal and hyperplastic prostate epithelial and stromal cell lines. In vitro experiments with the human neonatal prostatic epithelial cell line 267B-1 showed that calcitriol inhibited cell growth irrespective of DHT, indicating that the anti-proliferative effects of vitamin D are at least partly androgen-independent.[33]

5.2 Induction of Apoptosis

Calcitriol promotes apoptosis in prostate cells through both intrinsic (mitochondrial) and extrinsic (death receptor) pathways. Pro-apoptotic effects are mediated partly through downregulation of anti-apoptotic Bcl-2, which is expressed in BPH cells and suppresses mitochondria-mediated cell death. Analogue V (1,25-dihydroxy,16ene,23yne D_3) have been shown to decrease Bcl-2 expression in BPH cells, enhancing apoptotic susceptibility and reducing paracrine and autocrine growth factor signalling.[7] Calcitriol additionally activates caspase cascades and upregulates pro-apoptotic Bax and Bak proteins, collectively shifting the proliferation-apoptosis balance within hyperplastic prostatic cells towards programmed death.[34]

5.3 Inhibition of Growth Factor-Induced Proliferation

Calcitriol inhibits BPH cell proliferation not only under basal conditions but also when stimulated by established growth factors including IL-8, Des(1-3)IGF-1, testosterone, and DHT.[7] This broad inhibitory profile makes calcitriol particularly attractive as a preventive agent. Clinical evidence confirms that vitamin D analogues of upto 6,000 IU/day reduced prostate volume in BPH patients, and increasing dietary vitamin D intake was correlated with decreased BPH prevalence.[7] [35]

5.4 Interaction with Androgen Signalling

Calcitriol modulates AR expression and activity in prostate cells.[16] Specifically, $1,25(OH)_2D_3$ promotes androgen inactivation by inducing CYP3A4 and SULT2B1b, while androgen signalling reciprocally inhibits calcitriol degradation by suppressing CYP24A1.[32] This bidirectional regulation means vitamin D and androgens exert mutually modifying effects within the prostate. The ability of calcitriol to attenuate AR-mediated transcriptional activity represents an additional layer of anti-proliferative benefit, and may also explain why vitamin D status

influences clinical responsiveness to anti-androgenic therapies.

6. Vitamin D Deficiency, LUTS, and BPH: Clinical Evidence

6.1 Epidemiological and Cross-Sectional Studies

A case-control study by Elshazly et al. enrolled 70 men over 50 years with LUTS and 80 age-matched controls, finding significantly lower mean serum vitamin D levels in the LUTS group (40.82 ± 29.46 nmol/L vs 70.25 ± 22.42 nmol/L, $p < 0.001$) and significantly larger prostate volumes (50.12 ± 23.24 g vs 30.68 ± 4.90 g, $p < 0.001$).[6] A cross-sectional study by Reddy et al. among 175 men identified a significant negative correlation between serum vitamin D and total PSA ($r = -0.245$, $p = 0.022$), with vitamin D-deficient individuals showing markedly elevated PSA levels (12.57 ± 5.22 ng/mL). ROC analysis identified a serum vitamin D cut-off of 20 ng/mL as a diagnostic marker for BPH with 86% sensitivity.[5]

Among men with type 2 diabetes mellitus, Caretta et al. demonstrated an independent and significant inverse correlation between serum 25(OH)D levels and IPSS scores ($R = -0.333$, $p = 0.006$) and prostate volume ($R = -0.311$, $p = 0.011$) after multivariate adjustment, establishing hypovitaminosis D as an independent predictor of BPH severity.[36] A study of 612 men by Park et al. further found that vitamin D levels positively correlated with total testosterone but were significantly lower in patients with metabolic syndrome.[37]

6.2 Vitamin D and Overactive Bladder/LUTS

Yoo et al. studied 3,040 men with LUTS, finding that lower serum 25(OH)D was significantly associated with higher OABSS(Overactive Bladder Symptom Score) on multivariate analysis, with the strongest association in winter months when vitamin D status is typically lowest.[38] Vitamin D supplementation yielded significant dose-dependent improvements in OABSS in deficient patients. A prospective study by Yeo et al. administered 25,000 IU cholecalciferol every two weeks for one year in vitamin D-deficient men over 40 years, resulting in significant reductions in postvoid residual urine volume and total IPSS scores, with prostate volume stabilised compared to significant growth in the control group.[39]

6.3 Randomised Controlled Trial Evidence

The landmark RCT by Eftekhari et al. enrolled 108 men over 50 years with mild BPH symptoms and randomised them to 50,000 IU vitamin D_3 or placebo every two weeks for six months.[8] Prostate volume was significantly reduced and IPSS scores significantly improved in the intervention group ($p < 0.001$), with PSA levels also significantly lower than placebo. A Bangladeshi observational study confirmed significant reductions in prostate volume (from 33.8 ± 3.4 mL to 29.0 ± 3.2 mL, $p < 0.001$) and median IPSS (from 14.0 to 10.0, $p < 0.001$) following oral vitamin D supplementation across all BMI groups.[40]

7. Vitamin D Analogues and Therapeutic Development

The recognition of calcitriol's multi-target actions in BPH has spurred development of synthetic VDR agonists designed to retain therapeutic potency while minimising hypercalcaemia. Elocalcitol (BXL628) is the most extensively studied agent. In a Phase III randomised trial of 542 men with symptomatic BPH (baseline prostate volume 60–70 cc, IPSS 16–17), elocalcitol at 150 µg/day reduced prostate growth by 85% compared to placebo (0.52% increase vs 3.52%, $p < 0.0001$), significantly improved IPSS by five to six points, and improved Qmax, with lower adverse events than placebo.[41]

Mechanistic studies confirm that elocalcitol inhibits IL-8-dependent BPH stromal cell proliferation and invasion, suppresses NF-κB p65 translocation, reduces COX-2 and PGE_2, and blocks RhoA/MYPT-1 signalling.[23] BXL353, another low-calcaemic analogue, inhibited KGF-induced BPH cell proliferation and induced apoptosis.[31] CH5036249, a novel non-secosteroidal VDR agonist, demonstrated efficacy in a spontaneous BPH beagle model.[42] Combining VDR agonists with established BPH treatments — particularly 5-alpha-reductase inhibitors — has been proposed as a synergistic strategy targeting androgenic, inflammatory, and vitamin D-regulated axes simultaneously.[3]

8. Discussion

The evidence assembled in this review provides a compelling, multi-layered rationale for the immunomodulatory and anti-proliferative importance of vitamin D in BPH. BPH pathogenesis is increasingly understood as a disease with two inseparable axes: one androgenic and one inflammatory. The androgen-driven axis, mediated by DHT and 5-alpha-reductase, promotes cellular proliferation and suppresses apoptosis; the inflammatory axis, driven by chronically activated $CD4^+$ lymphocytes and macrophages, sustains a pro-proliferative cytokine microenvironment within the prostate. Vitamin D, through calcitriol and VDR-mediated signalling, intersects with and modulates both of these axes simultaneously, representing a uniquely positioned therapeutic molecule.

At the molecular level, calcitriol's inhibition of NF-κB signalling represents perhaps its most therapeutically significant anti-inflammatory action. NF-κB serves as a transcriptional hub integrating signals from multiple

cytokines, growth factors, and immune stimuli, driving the expression of IL-6, IL-8, COX-2, and numerous adhesion molecules that collectively sustain the BPH microenvironment.[23] By interrupting this central coordinator, VDR agonists achieve suppression of dozens of downstream mediators simultaneously — a pharmacological advantage over agents targeting single cytokines. This contrasts favourably with current BPH therapies, which act on androgen or adrenergic pathways only, without addressing the inflammatory component.

The RhoA/ROCK inhibitory mechanism of calcitriol adds a further therapeutic dimension, particularly relevant to the dynamic component of BPH. Smooth muscle hypertonia within the prostate and bladder neck contributes substantially to urinary outflow obstruction and overactive bladder symptoms, and is the primary target of alpha-adrenoceptor antagonists. The finding that VDR agonists suppress RhoA activation and MYPT-1 phosphorylation in BPH stromal and bladder smooth muscle cells suggests that vitamin D may be able to address both the inflammatory and smooth muscle components of LUTS from a single molecular platform.[17] [26] This property could make VDR agonists particularly beneficial in patients with mixed storage and voiding symptoms.

Immunologically, the shift induced by calcitriol from a Th1/Th17-dominated inflammatory infiltrate towards a regulatory T cell phenotype reflects a mechanism seen across multiple chronic inflammatory diseases managed with vitamin D. The reduction of macrophage M1 polarisation and the downregulation of IFN-γ, TNF-α, and IL-17 collectively attenuate the immune-stromal crosstalk that sustains BPH growth.[28] [29] Notably, these immunomodulatory effects are not merely antiproliferative but genuinely disease-modifying, targeting the upstream immunological drivers of BPH rather than downstream structural consequences.

The clinical translation of these laboratory findings is increasingly substantiated. The Phase III elocalcitol trial demonstrating up to 85% inhibition of prostate growth over six months,[41] combined with the RCT data from Eftekhari et al. showing significant volumetric and symptomatic improvement with cholecalciferol supplementation,[8] and the observational findings across multiple cross-sectional cohorts,[6] [36] [37] provide convergent clinical evidence that vitamin D status meaningfully influences prostatic biology in living patients. The dose-dependent nature of vitamin D's effects on OABSS observed by Yoo et al.[38] further reinforces a direct biological rather than merely associative relationship.

Nonetheless, several important limitations and research gaps deserve acknowledgment. The optimal serum 25(OH)D threshold for prostate protection remains undefined; current evidence suggests that levels above 30 ng/mL are associated with BPH benefit, but whether even higher levels(>60ng/mL) confer additional protection is unknown.[43] VDR gene polymorphisms introduce pharmacogenomic heterogeneity that may explain inconsistencies across clinical studies and should be incorporated into future trial stratification.[22] The dose and duration of supplementation required to achieve meaningful volumetric BPH regression — as opposed to merely slowing progression — remain to be established through long-term trials. The Yeo et al. study found prostate volume stabilisation rather than reduction after one year, suggesting that volumetric effects may require longer treatment windows.[39] Additionally, the interaction of vitamin D with concomitant BPH medications, particularly 5-alpha-reductase inhibitors and alpha-blockers, has not been prospectively studied in well-powered trials, and preclinical synergistic data require clinical validation.

The safety profile of vitamin D supplementation in the context of BPH is reassuring. Across all reviewed supplementation studies, no significant adverse effects or hypercalcaemia were reported at therapeutic doses.[7] [8] [40] Synthetic VDR agonists such as elocalcitol and CH5036249, specifically engineered to dissociate anti-proliferative from hypercalcaemic effects, also demonstrated favourable tolerability in clinical and animal studies.[41] [42] This safety margin is clinically important given that BPH predominantly affects older men, who have heightened sensitivity to hypercalcaemia.

Looking forward, the integration of vitamin D status assessment into routine BPH evaluation, the identification of VDR genotype as a precision medicine biomarker, and the development of next-generation non-calcaemic VDR agonists represent promising translational priorities. The potential for vitamin D to serve not only as a treatment adjunct but as a chemopreventive agent — reducing the incidence of BPH in men at risk through lifestyle modification and supplementation — has significant public health implications given the near-universal prevalence of the disease in elderly men worldwide.[44] [45] Well-designed Phase III trials with long follow-up, VDR genotyping, and combination therapy arms are now needed to fully define vitamin D's clinical role in BPH management.

9. Conclusion

Vitamin D exerts biologically significant immunomodulatory and anti-proliferative effects in

BPH through VDR-dependent mechanisms that are distinct from, yet complementary to, classical androgenic pathways. The suppression of NF-κB signalling, inhibition of the RhoA/ROCK cascade, modulation of T lymphocyte and macrophage phenotypes, induction of cell cycle arrest and apoptosis, and attenuation of growth factor-driven proliferation collectively position vitamin D as a multi-target agent against the chronic inflammatory and proliferative processes that define BPH pathogenesis. Clinical trials confirm that vitamin D supplementation reduces prostate volume and improves LUTS, and synthetic VDR agonists such as elocalcitol demonstrate potent anti-inflammatory and anti-proliferative efficacy in BPH tissue.

Further well-designed randomised controlled trials are warranted to establish optimal dosing regimens, treatment durations, and patient selection criteria for vitamin D in BPH. Investigations incorporating VDR genotyping and combination strategies with existing BPH pharmacotherapies are needed to advance clinical translation. In the interim, correction of vitamin D deficiency in men at risk for or presenting with BPH should be considered as part of a holistic, multi-target management approach.

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