Review Article

Vitamin D receptor as a therapeutic target for benign prostatic hyperplasia

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ABSTRACT

The bioactive form of vitamin D, 1α, 25-dihydroxyvitamin D3 (1α, 25(OH)2D3), is a secosteroid hormone that binds to the vitamin D receptor (VDR), a member of the nuclear receptor super-family expressed in many cell types, and modulates a variety of biological functions. 1α, 25(OH)2D3 is essential for bone and mineral homeostasis, but also regulates growth and differentiation of multiple cell types, and displays immunoregulatory and anti-inflammatory activities. The antiproliferative, prodifferentiative, antibacterial, immunomodulatory and anti-inflammatory properties of synthetic VDR agonists could be exploited to treat a variety of chronic inflammatory and autoimmune diseases, including benign prostatic hyperplasia (BPH). It has been hypothesized that VDR may influence both the risk of a variety of diseases and their occurrence and prognosis. However, earlier studies investigating the associations between specific VDR polymorphisms and various diseases often show controversial results. We performed a systematic review of the current literature on vitamin D and BPH using the PubMed and Web of Knowledge databases. The aim of this review is to summarize the current knowledge on the utility of the VDR gene regarding prostate growth as well as the pathogenesis and treatment of BPH, a complex syndrome characterized by a static component related to prostate overgrowth, a dynamic component responsible for urinary storage symptoms, and an inflammatory component. Despite the massive advances in recent decades, further research is needed to fully characterize the exact underlying mechanisms of VDR action on BPH and to comprehend how these cellular changes translate into clinical development in physical concert.

Key words: Benign prostatic hyperplasia, vitamin D receptor, therapy

BENIGN PROSTATIC HYPERPLASIA

Benign prostatic hyperplasia (BPH) is the most common benign neoplasm in aging men and a frequently occurring chronic condition in the male population, with a histological prevalence at autopsy of 50% in men between the ages of 50-60 years and of 90% prevalence in men over 80 years.[1] It is a complex and multifactorial disease from the etiological and pathophysiological point of view. According to AUA guidelines, there is an increase in the incidence of BPH worldwide and a growing public health concern in Asian countries.[2] Clinical BPH refers to the lower urinary tract symptoms (LUTS) associated with benign prostatic enlargement leading to bladder outlet obstruction.[3] BPH is defined histologically by hyperproliferation of stromal and epithelial cells of the prostate, caused by complex cellular alterations including changes in proliferation, differentiation, apoptosis and senescence.[4] Many epidemiological studies have been conducted worldwide over the last few decades, but the prevalence of clinical BPH remains difficult to determine. There are several lines of evidence suggesting a potential role of vitamin D in the development of BPH. Vitamin D3 is the form of vitamin D, and some of its analogs have been described as potent regulators of cell growth and differentiation of prostatic cells,[5] as vitamin D_3 binds to the vitamin D receptor (VDR), a member of the nuclear receptor super family, and modulates a variety of biological functions.[6]

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Quick Response Code:

Website: www.indianjurol.com

DOI: 10.4103/0970-1591.105745

This review summarizes the basic and clinical evidence of an association between VDR status and BPH, and describes how VDR affects prostate growth. Finally, we discuss potential VDR gene variants and their relationship to BPH, and touch on the effects of VDR on the pathogenesis of BPH and its therapeutic value.

1α, 25(OH)2D3 AND VDR

Vitamin D is produced in the skin by the enzymatic modification of cholesterol after exposure to ultraviolet B radiation. 1α,25-dihydroxyvitamin D3 (1α, 25(OH)2D3), the active form of vitamin D, is produced in the kidney by hydroxylation of its precursor, 25-hydroxyvitamin D3 (25(OH)D3), and plays a central role in calcium homeostasis and bone remodeling.[7] The biological effects of 1α, 25(OH)2D3 are mediated by its receptor, the vitamin D receptor (VDR), a member of the super-family of nuclear receptors (NRs). The VDR gene is located on human chromosome 12 and its structure is shown in Figure 1. In response to hormone binding, the VDR regulates the transcriptional activity of 1, 25$(OH)_2 D_3$-responsive genes by complexing with a vitamin-D response element located in the promoter region of target genes.[8]

Several polymorphisms have been identified in the VDR gene, and their functional significance and potential effects on disease susceptibility have been investigated.[9] Since the discovery of VDR expression in cells regulating the immune response, 1α,25$(OH)_2 D_3$ was shown to be beneficial in a variety of models of autoimmune and chronic inflammatory diseases. In addition, recent epidemiological studies correlate autoimmune disorders with low 25(OH) D_3 serum levels.[10] Since the supraphysiological doses of 1α,25(OH)2D3 required to demonstrate the stout anti-inflammatory effects also stimulate hypercalcemia, vitamin D analogs were synthesized in order to potentiate the anti-inflammatory properties of VDR agonists without inducing the hypercalcemic side effects.[11]

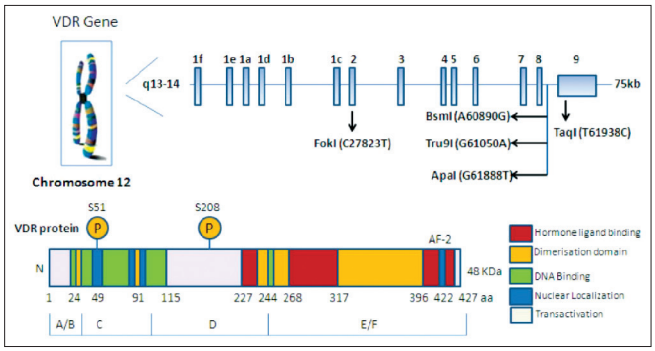

Figure 1: Chromosomal and protein domains of the Vitamin D receptor. The human VDR gene located on chromosome 12q, is composed of nontranslated exons (A-F) and exons 2-9, which encode 6 domains (A-F) of the full-length VDR protein. VDR associates with RXR through the dimerization domains (yellow). The 1α,25(OH)2D3–VDR–RXR complex binds to VDREs through the DNA-binding domain in the regulatory region of target genes. FokI, BsmI, ApaI, TaqI and Tru9I (SNPs) have been identified in VDR

ROLE OF VITAMIN D/VDR IN PROSTATE GROWTH

VDR is not only expressed in bone, bowel, and kidney but also in numerous additional human tissues, including those derived from the urogenital sinus, for instance the prostate and bladder.[12] It has pleiotropic effects that go beyond its traditional role in calcium homeostasis. Numerous genes with VDR response elements directly or indirectly affect the cell cycle, proliferation, differentiation and apoptosis.[13] The noncalcemic actions of vitamin D influence normal and pathological cell growth of various organs including prostate.[13] The presence of VDR in the human prostate was revealed in 1992.[14] Later, VDR was found in various types of cultured prostate stromal and epithelial, normal, cancerous and BPH cells and in different prostate cancer cell lines.[5,15] According to the immunohistochemistry data, there are significant variations in individual VDR levels in prostate samples from patients.[16] VDR ligands and other hormones, and growth factors that do not bind to the VDR, regulate the intracellular levels of VDR in a target cell [Figure 2]. It was shown that calcitriol increases VDR protein level in virtually all tissues including prostate, probably via ligand-dependent stabilization of the VDR by proteosomal degradation.[17] Vitamin D metabolites inhibit the growth of normal and malignant prostate cells as demonstrated in primary cultures, BPH, prostate cancer cell lines, xenograft models, and *in vivo* on rat prostate.[5,18] On the other hand, a study from Korea in BPH patients reported that high PTH, vitamin D, and calcium levels are not involve in prostate growth.[19]

VDR GENE VARIANTS AND BPH

Vitamin-D is involved in a wide variety of biological processes and its activity is mediated by VDR.[20] Variations in this receptor have been linked to more than a few common diseases, including prostate and bladder cancer, diabetes, urolithiasis, and tuberculosis, etc.[21] Previously we reported

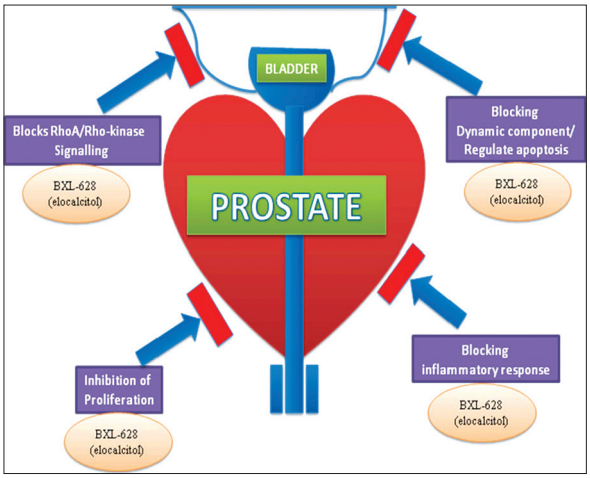

Figure 2: Schematic picture showing the role of vitamin D, calcitriol on intracellular signaling through a cascade of mediators and the possible consequences to BPH

that the frequency and distribution of VDR gene variants is substantially different in diverse populations and ethnic groups.[22] Genetic studies with respect to the VDR gene will definitely provide exceptional opportunities to connect molecular insights with epidemiological data and may reveal reticent and subtle, but true biological effects. The VDR gene variants are associated with a range of biological diseases including prostate growth. VDR is expressed in normal as well as malignant prostate cell.[15] It has been hypothesized that different SNPs in the VDR may influence BPH risk and many polymorphisms in the VDR gene have been identified through PCR-RFLP, among which Fok1, Bsm1, Apa1, Taq1, and Poly(A) have been studied the most frequently.[20] To date, few epidemiological studies have investigated the VDR gene polymorphisms in relation to BPH risk.[23]

Over the last few decades, VDR gene variants have been broadly investigated in several prostatic diseases and appear to have an important association with the disease risk. Activation of the VDR gene may influence androgen receptor (AR) activation leading to the development of BPH and thus VDR gene variants have been investigated in BPH for many decades. Habuchi *et al.* estimated the risk of BPH with VDR gene polymorphism for the first time and reported a significant association.[24] VDR genotypes have been associated with the risk of prostatic enlargement in BPH in Japanese men[25] There was a positive correlation between VDR gene variants and prostate volume.[26] Our group recently reported a statistically significant association between VDR genotype (Taq-I and Bsm-I) and BPH. It is also the first to report that VDR genotypes, specifically the Taq-I polymorphic variant, is significantly associated with the improvement of BPH patients with standard drug therapy.[27] By contrast, other reported no association between VDR gene polymorphism and the risk of BPH.[28] Nevertheless, modification of BPH susceptibility by certain VDR polymorphisms supports the notion that the VDR pathway, and therefore vitamin D, may modify BPH risk.

EFFECT OF VITAMIN D RECEPTOR LIGANDS AND AGONISTS ON BPH

Growth of the prostate gland is not only controlled by androgens, but also by the balance between programmed cell death and cell proliferation, which illustrate that prostate growth is regulated by both androgens and growth factors with coordination from several other factors. Alteration in the molecular mechanisms of these two processes may underlie the abnormal growth of the prostate, leading to BPH. Therapeutic approaches to the management of BPH can be broadly divided into antiadrenergic and antiandrogenic treatments.[29]

α1-adrenoceptor antagonists and 5α-reductase inhibitors are well-established treatment regimens for BPH. However, the long-term application of these drugs can lead to unpleasant side effects. Currently, there is a lack of preventive medication for asymptomatic BPH that retards the enlargement of the prostate and LUTS development. Apart from these approaches, new approaches with novel targets are evolving. The initiation of new therapies is, however, more slanting toward the static component, which involves metabolic factors such as hexokinase inhibitors, growth factors (vitamin D3 analogs), oxytocin antagonists, and gonadotropin- releasing hormone Gi agonist-based therapies. VDR agonists are apparently more efficacious for symptom relief than for the reduction of prostate volume in human BPH. Carsten *et al.* 2006, based on crystal structure data, molecular dynamics simulations, and biochemical assays, have discussed a detailed molecular understanding of the agonistic and antagonistic actions of VDR ligands.[30]

BXL-628

In particular, BXL-628 (elocalcitol) decreased testosterone (T)-stimulated human BPH cell proliferation similarly to finasteride and cyproterone acetate, and promoted BPH cell apoptosis even in the presence of growth factors. However, this analog does not consistently impede androgen receptor (AR) signaling. The preclinical and clinical data reviewed here show that BXL-628 is able to inhibit prostate growth, and indicate its ability to control prostate inflammation. Different mechanisms of action account for the capacity of BXL-628 to reduce the static component of BPH, from the induction of apoptosis in prostate cells to the inhibition of intraprostatic growth factor activity downstream of the AR. Adorini *et al.* 2006 documented the anti-inflammatory effects of BXL-628 in animal models of autoimmune prostatitis, observing a significant reduction of intraprostatic cell infiltrate following the administration of this VDR agonist at normocalcemic doses.[31]

BXL-628 inhibits RhoA/Rho-kinase signaling, a calcium-sensitizing pathway, suggesting its possible clinical use in the treatment of altered bladder contractility often associated with BPH-induced LUTS. This information extends the potential use of VDR agonists to novel indications that symbolize significant unmet medical needs, and offer a sound rationale for further clinical testing.

ELOCALCITOL

Elocalcitol is a synthetic derivative of vitamin D3 that regulates cell proliferation and apoptosis. Earlier reports elucidated that elocalcitol-repressed androgen reliant and independent proliferation of BPH cells more potently than finasteride, a 5μ-reductase inhibitor. In a phase IIb trial in patients with BPH, elocalcitol significantly reduced prostate volume compared with the placebo group. In another phase IIa trial it extensively abridged levels of IL-8 in semen in a group of prostatitis patients, telling improved quality and forward motility of sperm.[32]

However, it has not shown to be effective in a phase IIb trial with overactive bladder (OAB), which led to the termination of its further clinical development. With its novel mechanism of action, efficacy profile, and improved tolerability over the on-hand classes of drugs, this compound could have been potentially added to the armamentarium in the expanding therapeutic markets of BPH and OAB.[29]

Elocalcitol reduces the static component of BPH by inhibiting the activity of intraprostatic growth factors downstream of the AR. It reduces the dynamic component by targeting the RhoA/ROCKpathway in prostate and bladder cells, and the inflammatory component by targeting the NF-kB pathway.[33] A recent report suggests that prostatic urethra is within the lower urinary tract, a novel target for VDR agonists, as shown by the capacity of elocalcitol to inhibit ROCK activity and to limit inflammatory responses in human primary urethra cells.[34]

CH5036249 is also a novel nonsecosteroidal VDR agonist, exhibits favorable characteristics with potential as a new drug candidate for the treatment of BPH. Taniguchi *et al*., in 2010 demonstrated that CH5036249, a possible innovative drug candidate for the treatment of BPH and whether or not it improves symptomatic parameters in the clinical setting of human BPH is extremely fascinating.[35]

CALCITRIOL

The active hormonal form of vitamin D, 1α, 25-dihydroxyvitamin D3 (calcitriol), plays a critical role in the cellular proliferation and differentiation of normal and malignant cells. VDRs are not only expressed in normal but also in hyperplastic and cancerous prostate[5] therefore, calcitriol has potential for the therapeutic management of BPH and prostate cancer.

However, the therapeutic applicability of calcitriol is inadequate due to the additional effects of hypercalcaemia and hyperphosphataemia. Therefore, the analogs of calcitriol that retain the antiproliferative properties but do not cause the side effects of hypercalcaemia *in vivo* were developed.[36] Chronic inflammation is now considered a determinant of BPH, promoting, collectively with the hormonal conditions, prostate overgrowth and lower urinary tract symptoms (LUTS). Calcitriol can also promote innate immunity and regulate adaptive immune responses, being potentially useful in the treatment of inflammatory diseases like BPH.[37]

Overall, VDR agonists can modify the dynamic component of LUTS pathogenesis and exert anti-inflammatory activities. Thus, this class of agents could symbolize an interesting therapeutic alternative for the pharmacological treatment of BPH. Vitamin D has astonishing potential as a therapeutic agent in BPH treatment. However, there have not yet been any outsized clinical trials using vitamin D or its analogs to treat BPH. At present, several vitamin D analogs are under investigation, but none have been found to be effective without causing side effects. Since vitamin D acts primarily via the VDR, genetic polymorphisms of the VDR gene may affect vitamin D function and individual genetic characteristics should be considered when using vitamin D to treat BPH. This may maximize the efficacy of vitamin D analogs and minimize the side effects.

CONCLUSIONS

VDR has emerged as a vital factor in BPH with newly ascribed autocrine functions vastly different from its classical function in mineral homeostasis. Therefore, to ignore the connotation of VDR and its potential impact on morbidity and mortality in the BPH patient is no longer appropriate. Experimental evidence also proves the immunomodulatory role of VDR ligands in the pathogenesis of BPH. Therefore, vitamin D or its analogs may have the best utility as chemopreventive agents in BPH. Studies in animal models also suggest that vitamin D agonists are more effective when administered before, rather than subsequent to, the initial occurrence of BPH. Based on the evidence presented, we believe that Vitamin D and its analogs deserve further evaluation in clinical trials among BPH patients with different stages of the disease. Eventually, combination therapies with 1α25(OH)2D3 compounds need to be explored for better and more effective therapy of BPH. These observations emphasize the need for better awareness among researchers, clinicians, and patients of the high prevalence of vitamin D inadequacy and a more aggressive screening for vitamin D/VDR status, particularly among high-risk populations such as elderly patients and patients with BPH.

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How to cite this article: Manchanda PK, Kibler AJ, Zhang M, Ravi J, Bid HK. Vitamin D receptor as a therapeutic target for benign prostatic hyperplasia. Indian J Urol 2012;28:377-81.

Source of Support: Nil, **Conflict of Interest:** None declared.