

Vitamin D and benign prostatic hyperplasia - a review

Geovanni Espinosa, ND, Ralph Esposito, Amir Kazzazi, MD, Bob Djavan, MD

Department of Urology, New York University School of Medicine, New York, New York, USA

ESPINOSAG, ESPOSITOR, KAZZAZIA, DJAVAN B. Vitamin D and benign prostatic hyperplasia - a review. *Can J Urol* 2013;20(4):6820-6825.

Introduction: Benign prostatic hyperplasia (BPH) is a more common form of lower urinary tract symptoms (LUTS). BPH is due to the excessive growth of both stromal and epithelial cells of the prostate. Fifty percent of men over the age of 50 will have this disease, along with the probability that 90% of men at the age of 80 will have an enlarged prostate. The prevalence of vitamin D deficiency in the male urological population may represent a connection between BPH and vitamin D.

Material and methods: This review is geared to provide the most relevant data on the correlation between vitamin D and BPH. A comprehensive review was conducted on all studies on the specific topic and compiled into a complete article.

Results: Data suggests that vitamin D has an inhibitory effect on the RhoA/ROCK pathway, along with cyclooxygenase-2 expression and prostaglandin E2 production in BPH stromal cells. Increasing intake of vitamin D from diet and supplements has shown a correlation with decreased BPH prevalence. Vitamin D analogues of up to 6000 IU/day have shown to decrease prostate volume in BPH patients. Pre-clinical trials have shown vitamin D to not only decrease BPH cell and prostate cell proliferation alone, but also when induced by known growth promoting molecules such as IL-8, Des (1-3) IGF-1, testosterone and dihydrotestosterone. Among all the studies there has not been any side effects or negative implications with increased vitamin D intake.

Conclusion: The impact of vitamin D on prostate volume and BPH has shown promising results, thus proposing further studies on vitamin D and BPH be conducted.

Key Words: vitamin D, benign prostatic hyperplasia, prostate, nutrition

Introduction

Vitamin D₃, molecularly known as 1,25-dihydroxyvitamin D₃, has recently been gaining exposure in science for its impact on disease states. Evidence shows that from 1988 to 2004 serum vitamin D levels among Americans has significantly decreased.¹ With this trend, there is a potential risk of vitamin D deficiency, which may potentially lead to health complications considering its metabolic functions in the human body.

With vitamin D slowly becoming the vitamin of the decade, its importance in the diet and its relationship to disease are becoming a concern for doctors. Vitamin D serum levels are becoming a staple of most blood tests, which suggests increased attention on vitamin

D levels and its association with illnesses. Yet the Institute of Medicine (IOM) and the Endocrine Society cannot distinctly provide recommendations for daily vitamin D intake and serum vitamin D levels.² This leaves many physicians to formulate their recommendations to each individual patient. There has been a special focus on vitamin D serum levels in the urological population, which has found 34.3% of men have serum 25(OH)D levels less than 20 ng/mL.³ Recent studies have even shown an inverse correlation between the geographic distributions of prostate cancer and the geographic exposure to UV radiation.⁴ The prevalence of vitamin D insufficiency (< 30 ng/mL) is more common in the winter months, along with prostate cancer being more prevalent among those deficient in vitamin D.⁵

A common form of lower urinary tract symptoms (LUTS) in men is benign prostatic hyperplasia (BPH). Defined by the American Urological Association, BPH is a cluster of symptoms affecting older men including obstructive symptoms such as decreased

Accepted for publication January 2013

Address correspondence to Dr. Geovanni Espinosa, Department of Urology, New York Langone Medical Center, 150 East 32nd Street, New York, NY 10016 USA

force of stream, hesitancy, straining, incomplete bladder emptying, and nocturia.⁶ BPH is due to the excessive growth of both stromal and epithelial cells of the prostate. Fifty percent of men over the age of 50 will have BPH, along with the probability that 90% of men at the age of 80 will have an enlarged prostate.⁷ With the prevalence of vitamin D deficiency in the male urological population this review aims at demonstrating that 1,25-dihydroxyvitamin D₃ (1,25(OH)₂D₃) and analogues may have an impact on BPH. The data for these relationships is scattered, and the use of vitamin D as a therapeutic nutrient requires a complete review to further identify these relationships.

Vitamin D can be utilized through the consumption of food as cholecalciferol (D₃) or ergocalciferol (D₂), supplements or upon skin exposure to sunlight. After ultraviolet B (UVB) exposure to the epidermis 7-dehydrocholesterol is converted to cholecalciferol, 25(OH)D. From here it is moved to the liver via vitamin D binding protein (DBP). At the liver, 25-hydroxylase (CYP2R1) catalyzes cholecalciferol to 25-hydroxyvitamin D₃ (25(OH)D₃), which is the major circulating form of vitamin D. As 25(OH)D₃ moves in the blood stream to the kidneys, hydroxylation is carried out again. 1 α -hydroxylase carries out hydroxylation to create 1 α ,25(OH)₂D₃.⁸ See Figure 1. The prostate has also been shown to hydroxylate 25(OH)D₃ to 1,25(OH)₂D₃.⁹

Vitamin D receptor (VDR) is a steroid receptor that helps regulate gene expression in cells. 25(OH)D₃ is bound to DBP and carried throughout the body. The DBP transports the vitamin D to cells where it may bind to receptors on the cell or it may enter the cell. As it enters the cell it is catalyzed into 1,25(OH)₂D₃ via 1 α -OHase. Now vitamin D may bind to the VDR, which is attached to the Vitamin D Responsive Element (VDRE) thus allowing transcription to be regulated. The VDR is a heterodimer with retinoic x receptors (RXR) and zinc is a key cofactor in connection between the VDR and VDRE. Here 1,25(OH)₂D₃ acts as a transcription factor and has a profound impact on gene expression.¹⁰ See Figure 2.

Mechanism of vitamin D₃ and analogues in BPH stromal cells

The mechanism as to how vitamin D and analogues impact BPH cells involves an inhibitory impact on proliferative response and inflammation. BPH cells exposed to IL-8, which induces BPH cell proliferation, were also exposed to vitamin D analogue elocalcitol, which have shown an inhibitory effect on the RhoA/ROCK pathway. A secondary mechanism included a

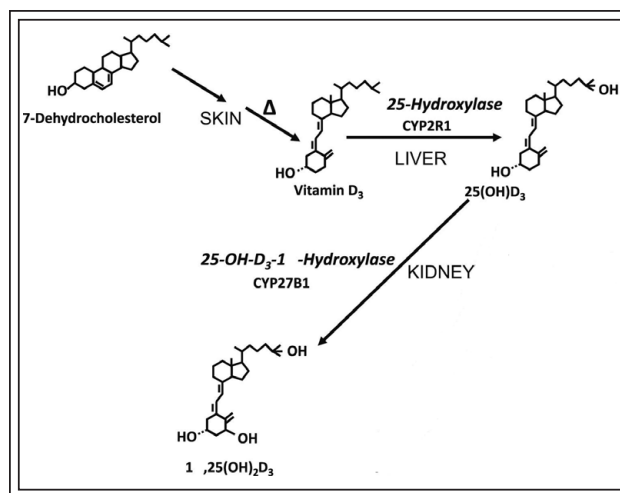


Figure 1. Metabolism of vitamin D₃ in the skin, liver and kidney. 7-dehydrocholesterol is converted to vitamin D₃ (cholecalciferol) in the skin via UV radiation. Vitamin D₃ is converted to 25-hydroxyvitamin D₃ (25(OH)D₃) in the liver via 25-hydroxylase. The 25(OH)D₃ circulates in the blood stream as it reaches the kidney to then be catalyzed by 1 α -hydroxylase (1 α -OHase) into 1,25-dihydroxyvitamin D₃.⁸ Reprinted by permission from Elsevier.

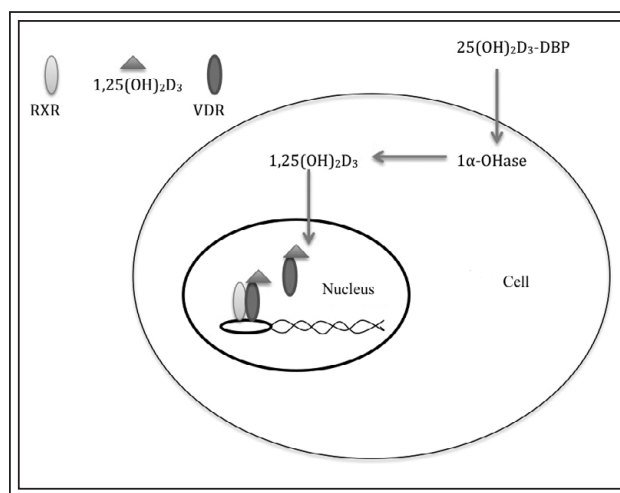


Figure 2. VDR and 1,25(OH)₂D₃ mechanism in gene expression. 25(OH)D₃ is bound to vitamin D binding protein (DBP) as it travels through the blood stream. The 25(OH)D₃ will enter the cell as it is catalyzed via 1 α -OHase into 1,25(OH)₂D₃. Here vitamin D₃ may enter the nucleus to bind to the vitamin D receptor (VDR) and then bind to the vitamin D responsive element (VDRE) as a heterodimer with retinoic x receptors (RXR). Thus impacting gene expression and transcription.¹⁰ Reprinted by permission from Macmillan Publishers Ltd.

reduced COX-2 expression and PGE2 production by inhibition of IL-8 via elocalcitol, along with an arrest of NF-κB p65 nuclear translocation. The data indicates the connection between IL-8 and BPH cell proliferation through various pathways, which can be targeted by elocalcitol.¹¹

Materials and Methods

Literature search

A systematic review of all literature was conducted in order to obtain the most accurate, precise and latest data regarding the relationship between vitamin D intake and BPH. The literature review includes papers, abstracts and review articles dating up to May 2012. The following electronic databases were used: Ovid and PubMed. Various key terms were utilized to ensure a comprehensive number of results with the most accurate results. The search terms were used to create highly sensitive results to avoid any erroneous data regarding other diseases or nutrients. Data was targeted primarily towards human trials however several animal studies showed promising results with potentially beneficial human applications.

Vitamin D analogs

Discussed in the articles, the purpose of using a vitamin D analog was for fear of hypercalcemia. Therefore the studies that did use a vitamin D analog, named them 'non-calcemic.' Analogs include BXL628 (elocalcitol), analogue V (1,25 dihydroxy, 16ene,23yne D₃ or Ro 23-7553), CH5036249 and BXL353.

Genetic factors and BPH pathogenesis

With the various reports studying the correlation between vitamin D and BPH, the genetic components have been unclear. Several studies have demonstrated

the impact of a genetic component of BPH with a link to the genetic variants of the VDR gene, Table 1.

The association of a specific VDR genotype and BPH in an Indian population was identified in the Taq-I and Bsm-I. These specific loci, in comparison to the Fok-I loci, showed a significant correlation in BPH patients (p = 0.022 and p = 0.033). Although this genotype may be evident, the patient's response to any treatment is also a factor. Therefore, 'responders' to treatment (as categorized as an improvement in Qmax (maximum flow), reduction in AUA score and post void residue within 6 months of 5α-reductase inhibitors and β-adrenergic blockers) showed a difference in the Taq-I genotype without any associations at other VDR loci (p = 0.001).¹²

An enlarged prostate, with a volume greater than 30 mL, has been identified in men exhibiting polymorphisms in the VDR gene. The homozygous C variant of the Taq-I genotype was identified in men with an enlarged prostate (p = 0.05). A presence of one or two variant C alleles was also associated with prostate volume (p = 0.04).¹³ The Bsm-I gene was positively associated with prostate volume with the presence of at least one A allele (p = 0.01), along with heterozygous GA (p = 0.04) and the homozygous A variant (p = 0.03). Therefore the data suggests men with the specific VDR polymorphisms are susceptible to increased prostate volume; thus these polymorphisms may be involved in BPH pathogenesis by encoding growth factors.¹⁴ The Taq-I VDR genotype may also be identified as t indicating the Taq-I polymorphism is present or as T indicating the Taq-I is absent. BPH patients with an increased prostate volume (> 50 mL) the TT genotype was statistically more frequent compared to control.¹³ Thus supporting previous research in identifying specific VDR polymorphisms may play a role in BPH.

Pre-clinical

Des (1-3) IGF-I, an IGF analogue, is a potent mitogen for BPH cells leading to increased proliferation of in

TABLE 1. VDR-gene loci in BPH participants. The table identifies which genes exhibited a polymorphism and which did not. All participants exhibited an enlarged prostate volume

VDR gene loci	Foc-I	Taq-I	Bsm-I
Manchanda et al ¹²	Polymorphism not present	Polymorphism present (also in 'responders')	Polymorphism present
Mullan et al ¹³	N/A	Polymorphism present	Polymorphism present
Hamasaki et al ¹⁴	N/A	Polymorphism not present	N/A

vitro BPH cells. Increasing concentrations, varying from 0.1-100 ng/mL of vitamin D analogue (V), showed a decrease in the promoting effect of BPH cells treated with Des(1-3) IGF-I.¹⁵ This was even shown at sub-picomolar concentrations. Analogue V-treated cells showed a 50.2% ± 0.9% of apoptotic nuclei, approximately 5-fold higher than in untreated cells (9.4% ± 0.9%, *p* < 0.001). Addition of analogue V to the Des (1-3) IGF-I exposed BPH cells counteracted the Des (1-3) effect (*p* = < 0.01). This indicates that the vitamin D analogue induced program cell death and lead to a decreased dcl-2 protein expression. It is hypothesized the anti-proliferative and pro-apoptotic activity of analogue V is due to the decreased expression of bcl-2, therefore able to decrease the paracrine/autocrine growth factors involved in BPH.¹⁵ 1 α ,25(OH)₂D₃ administered to untreated BPH cells showed a dose-dependent inhibition of human prostate stromal cell proliferation.¹⁶ Testosterone (T) induced BPH cells treated with vitamin D analogue BXL353 exhibited a reduced cell proliferation at subfemtomolar concentrations. Even at higher concentrations, BXL353 induced a significant decrease in proliferation (maximum inhibitory concentration,

65.8% ± 4.4%) even when compared with untreated control cells. Treatment with T significantly reduced the number of BPH cells committed to death, therefore the vitamin D analogue inhibited the mitogenic and antiapoptotic impact of testosterone on BPH cells.¹⁷

In beagle dogs treated with 0.03 µg/kg for 48 weeks, 2 out of 3 dogs showed a decreased rate in prostate growth, and prostate weight was slightly reduced. However in all models the BPH epithelial proliferation, as defined as the area of papillary proliferation to the entire prostate epithelium and as the ratio of the glandular area to the entire prostate, was reduced by the vitamin D analogue.¹⁸ Vitamin D analogue BXL353 administered to castrated mice treated with testosterone enanthate was able to reduce ventral prostate growth with maximal effect at 30 µg/kg. The same impact was observed in intact male rats at the same dosage of BXL353.¹⁶ The study suggests that vitamin D shows promising abilities to inhibit BPH cell proliferation and promote apoptosis even with testosterone exposure.

With bladder neck tissue and prostate showing virtually the same expression of VDR, the vitamin D analogue BXL-628 was shown to counteract the

TABLE 2. Vitamin D on BPH and prostate cells

Study	Subject	Outcome
Penna et al ¹¹	BPH cell culture	Increasing concentrations of elocalcitol inhibit dose dependent BPH cells proliferation induced by a fixed dose of IL-8.
Crescioli et al ¹⁵	BPH cell culture	Vitamin D analogue was able to completely block the growth promoting effect of increasing Des (1-3) IGF-I concentrations. The analogue impaired promoting activity of Des (1-3) IGF-I. At higher vitamin D analogue concentrations, BPH cell proliferation was below the basal level (<i>p</i> < 0.01 versus untreated cells).
Taniguchi et al ¹⁶	Prostate stromal cells	Increased concentrations of analog and vitamin D ₃ showed a dose-dependent inhibition of human prostate stromal cells, with vitamin D ₃ (calcitrol) showing superior results.
Crescioli et al ¹⁷	BPH cell cultures	Vitamin D ₃ analog BXL-353 abrogated the growth stimulatory effect of testosterone and at higher concentrations induced a significant decrease in proliferation. BXL-353 completely blocked both testosterone and DHT-stimulated BPH cell growth and significantly reduced cell proliferation.

TABLE 3. Benign prostatic hyperplasia (BPH) and vitamin D intake

a) In the Kristal study, evidence suggests an increased vitamin D intake is associated with a decreased risk of BPH. b) The Colli study, suggests that vitamin D administration may decrease prostate volume in BPH patients.

Study	Population	Outcome
Kristal et al ²⁰	Placebo-arm men participants free of BPH at baseline (n = 4770)	The highest quintile of total vitamin D intake (624 IU) had a 18% reduced risk of BPH compared to the lowest quintile intake (144 IU) (p = 0.032). Inverse correlation between BPH risk and supplemental vitamin D intake (p = 0.047)
Colli et al ²¹	Men age ≥ 50 years, diagnosis of BPH, prostate volume ≥ 40 mL (n = 119)	10 month administration of 6000 IU/day of vitamin D analogue resulted in a -2.90% change in prostate volume (p = < 0.0001)

impact of testosterone and dihydrotestosterone (DHT) induced human bladder cell growth by increasing apoptosis.¹⁸ Bladder neck cells derived from BPH patients showed (by androgen receptor (AR) mRNA abundance) BPH patients expressed similar levels of AR genes as other androgen-receptive tissues being 1 log unit lower than that of the prostate. Therefore the study suggests that due to bladder overgrowth and smooth muscle overactivity in patient's experiences with bladder decompensation and LUTS, the vitamin D analogue may be helpful in BPH patients for prostate and bladder help¹⁸ Table 2.

Oftentimes 25(OH)D₃ may be administered however its conversion to 1,25(OH)₂D₃ is the more essential information. When testing the active enzyme 1 α -hydroxylase in conversion of 25(OH)D₃ to 1,25(OH)₂D₃, BPH cells showed statistically significant lower levels of the enzyme (1.21 to 1.71 pmol/mg protein/h) in comparison to normal prostate cells.¹⁹ This may indicate that a normal serum vitamin D level may still leave the prostate and BPH cells deficient.

Human studies

Vitamin D consumed via the diet and supplements was studied in a BPH male population. Total vitamin D intake, including dietary and dietary supplements was associated with a reduced risk of BPH. A total intake of 15.6 μ g/day (624 IU), compared to the lowest quintile of < 3.6 μ g/day (144 IU) showed a 18% reduced risk of BPH (p = 0.032). With vitamin D supplementation only, there was a trend for decreasing BPH risk with increased vitamin D supplementation, showing consumption of > 11 μ g/day (440 IU) correlated with a decreased BPH risk (p = 0.047). The data suggests increasing

intake of vitamin D from diet and supplements or just supplements alone may have an impact on BPH prevalence.²⁰

Vitamin D and vitamin D analogues show promising results in treating men with BPH, even at untraditionally higher doses.²⁰ A doubled blind RCT showed men diagnosed with BPH and an enlarged prostate (> 40mL) showed a -2.90% decrease in prostate volume (p < 0.0001) after consuming 150 μ g/day (6000 IU) of vitamin D analogue BXL628 after 10 months. A total of 28.9% of men responded to the treatment, and 7.7% did not. With doses as high as 6000 IU, the changed in serum calcium levels was 0.04 mg/dL (not significant).²¹ The data suggests that even untraditionally high doses of vitamin D can decrease prostate volume in men with BPH. However the data did not show any significant changes in the Qmax (uroflowmetry), AUA SI score or serum PSA, Table 3.

Conclusions

The genetic component to vitamin D receptor and BPH has identified three different VDR gene loci that may give clues into BPH and the interaction with vitamin D. As shown in Table 1, two studies have identified polymorphisms in the Taq-I loci of BPH patients, whereas a third study did not identify any polymorphisms in the Taq-I. The Bsm-I loci has also been identified as a possible location for VDR gene polymorphisms in men with BPH. Although the data is not unanimous, it is important to observe that these loci play a role in the treatment of BPH with vitamin D. The variations in these loci at this point cannot point to a direct genetic cause of BPH, however it does permit further research into these VDR polymorphisms and their association with BPH.

The correlation of an increased intake of vitamin D and the decreased risk of BPH gives insight into the impact vitamin D may have on BPH patients.¹⁸ The highest quintile of vitamin D intake of 624 IU is on par with the RDA of 600 IU. This study however was showing just the correlation to the lowest quintile, and yet did not show an impact on other BPH parameters. A secondary human RCT showed that 6000 IU of vitamin D analogue decreased prostate volume by -2.90%.²¹ Therefore these two studies show that even at RDA doses of vitamin D there may be a therapeutic impact of BPH prevention, yet the studies also show that even at untraditionally high doses of 6000 IU there is potential for BPH treatment with vitamin D. It must not be ignored that the 6000 IU administered was a vitamin D analogue that was designed to have minimal impact of calcium homeostasis. Therefore, it is unknown as to whether 6000 IU of calcitrol will have an impact of calcium homeostasis, or whether 6000 IU of calcitrol is even necessary given lower doses may be just as beneficial. Further research is required to discover the impact of calcitrol in comparison to analogues.

The in vitro pre clinical trials have shown that vitamin D analogues and also calcitrol have impact on BPH and prostate cell proliferation. The various studies have shown vitamin D to not only decrease BPH cell and prostate cell proliferation alone, but also when induced by known growth promoting molecules such as IL-8, Des (1-3) IGF-1, testosterone and dihydrotestosterone. This promising data suggests that further research on human clinical trials is warranted.

In conclusion, the research does show potential for the use of vitamin D in treatment of BPH. Further research is required to identify specific doses for treatment. Given the vitamin D deficiency among Americans and the urological population, it is unknown as to whether a vitamin D deficiency may play a role in BPH and prostate health. The current research does not indicate any potential harm in vitamin D as a BPH treatment and it is reasonable to suggest that further vitamin D impact on BPH is warranted given its low risk and potential benefits. □

References

1. Ginde AA, Liu MC, Camargo CA Jr. Demographic differences and trends of vitamin D insufficiency in the US population, 1988-2004. *Arch Intern Med* 2009;169(6):626-632.
2. Hollis B. Short-term and long-term consequences and concerns regarding valid assessment of vitamin D deficiency: Comparison of recent food supplementation and clinical guidance reports. *Curr Opin Clin Nutr Metab Care* 2011;14(6):598-604.

3. Pitman MS, Cheetham PJ, Hruby GW et al. Vitamin D deficiency in the urological population: A single center analysis. *J Urol* 2011; 186(4):1395-1399.
4. Schwartz GG, Hanchette CL. UV, latitude, and spatial trends in prostate cancer mortality: All sunlight is not the same (United States). *Cancer Causes Control* 2006;17(8):1091-1101.
5. Choo CS, Mamedov A, Chung M et al. Vitamin D insufficiency is common in patients with nonmetastatic prostate cancer. *Nutr Res* 2011;31(1):21-26.
6. American Urological Association. Benign prostatic hypertrophy. Available from URL: <http://www.auanet.org/content/education-and-meetings/med-stu-curriculum/bph.pdf>. Accessed January 24th, 2012.
7. Sausville J, Naslund M. Benign prostatic hyperplasia and prostate cancer: an overview for primary care physicians. *Int J Clin Pract* 2010;64(13):1740-1745.
8. Henry HL. Regulation of vitamin D metabolism. *Best Pract Res Clin Endocrinol Metab* 2011;25(4):531-541.
9. Schwartz GG, Whitlatch LW, Chen TC et al. Human prostate cells synthesize 1,25-dihydroxyvitamin D₃ from 25-hydroxyvitamin D₃. *Cancer Epidemiol Biomarkers Prev* 1998;7(5):391-395.
10. Adorini L, Penna G. Control of autoimmune diseases by the vitamin D endocrine system. *Nat Clin Pract Rheumatol* 2008;4(8): 404-412.
11. Penna, G, Fibbi B, Amuchastegui S et al. The vitamin D receptor agonist elocalcitol inhibits IL-8-dependent benign prostatic hyperplasia stromal cell proliferation and inflammatory response by targeting the RhoA/Rho kinase and NF-kB pathways. *Prostate* 2009;69(5):480-493.
12. Manchanda PK, Konwar R, Nayak VL et al. Association of genetic variants of the vitamin D receptor (VDR) gene (Fok-I, Taq-I and Bsm-I) with susceptibility of benign prostatic hyperplasia in a north Indian population. *Asian Pacific J Cancer Prev* 2010;11(4):1005-1008.
13. Hamasaki T, Inatomi H, Katoh T et al. Significance of vitamin D receptor gene polymorphism for risk and disease severity of prostate cancer and benign prostatic hyperplasia in Japanese. *Urol Int* 2002;68(4):226-231.
14. Mullan RJ, Bergstralh EJ, Farmer SA et al. Growth factor, cytokine, and vitamin D receptor polymorphisms and risk of benign prostatic hyperplasia in a community-based cohort of men. *Urology* 2006;67(2):300-305.
15. Crescioli C, Villari D, Forti G et al. Des (1-3) IGF-I-stimulated growth of human stromal BPH cells is inhibited by a vitamin D₃ analogue. *Mol Cell Endocrinol* 2002;198(1-2):69-75.
16. Taniguchi K, Katagiri K, Kashiwagi H et al. A novel nonsteroidal VDR agonist (CH5036249) exhibits efficacy in a spontaneous benign prostatic hyperplasia beagle model. *J Steroid Biochem Mol Biol* 2010;121(1-2):204-207.
17. Crescioli C, Ferruzzi P, Caporali A et al. Inhibition of spontaneous and androgen-induced prostate growth by a nonhypercalcemic calcitriol analog. *Endocrinology* 2003;144(7):3046-3057.
18. Crescioli C, Morelli A, Adorini L et al. Human bladder as a novel target for vitamin D receptor ligands. *J Clin Endocrinol Metab* 2005; 90(2):962-972.
19. Hsu J, Feldman D, McNeal JE et al. Reduced 1 α -hydroxylase activity in human prostate cancer cells correlates with decreased susceptibility to 25-hydroxyvitamin D₃-induced growth inhibition. *Cancer Res* 2001;61(7):2852-2856.
20. Kristal AR, Arnold KB, Schenk JM et al. Dietary patterns, supplement use, and the risk of symptomatic benign prostatic hyperplasia: results from the prostate cancer prevention trial. *Am J Epidemiol* 2008;167(8):925-934.
21. Colli E, Rigatti P, Montorsi F et al. BXL628, a novel vitamin D₃ analog arrests prostate growth in patients with benign prostatic hyperplasia: a randomized clinical trial. *Eur Urol* 2006;49(1): 82-86.