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Deficiency of Vitamin D and Elevated Aldosterone in Prostate Hyperplasia

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Abstract

Background. Epidemiological studies have confirmed the association between vitamin D deficiency and benign prostate hyperplasia (BPH). Lately, serum calcium and parathyroid hormones were shown to stimulate prostate growth, assuming an interplay between elements of the calcium metabolism rather than a sole role of any. Finally, aldosterone actions were found to be affected by vitamin D.

Objectives. We have sufficient reason to believe that human disease, BPH in this case, is a dysfunction of a fine network rather than a failure of a particular substance. Unfortunately, previous studies include results of studies that fall short in combining the overall structure. This study aimed to investigate these four parameters in BPH patients.

Material and Methods. Twenty five patients with BPH (median age 62 years) and 30 volunteer healthy controls (median age 63.5 years) were enrolled. Serum total prostate specific antigen (PSA), intact parathormone (PTH), calcium, 25-hydroxy vitamin D (25-(OH) 2D), aldosterone and lipids were measured.

Results. We found serum aldosterone levels significantly higher in BPH patients ($p = 0.04$). BPH patients had significantly higher serum PSA levels ($p < 0.0001$). 25-(OH) 2D levels were lower in the BPH group ($p = 0.05$). Median serum 25-(OH) 2D levels in both groups were lower than the threshold reference limit (20 ng/mL).

Conclusions. The co-existence of vitamin D deficiency and elevated levels of aldosterone in BPH, presented for the first time in literature, strongly favors a link between the renin-angiotensin system (RAS), vitamin D and BPH pathogenesis. Our findings may influence studies with larger groups of subjects (*Adv Clin Exp Med* 2014, 23, 3, 441–446).

Key words: ALDO, aldosterone, BPH, prostate, vitamin D.

Benign prostatic hyperplasia (BPH) is the non-malignant overgrowth of prostatic glandular and stromal tissue, leading to the enlargement of the gland that eventually blocks the flow of urine through the urethra. Although a long-known disease, the exact etiology of BPH is still obscure. In daily practice, BPH is not considered a life-threatening condition, yet the symptoms it causes may drastically reduce the quality of the patient's life [1].

Medical records present histologically-proven BPH in about 8% of men in their third decade of life. The prevalence increases with age reaching to about 90% by the ninth decade. BPH is apparently a chronic disease, indolent, but doggedly persistent

through years that span decades [1]. As any disease with a high frequency in the elderly, BPH is usually present with one or more comorbidities. The prevalence of cardiovascular disease (CVD) and hypertension (HT) in aging men may also relate in part to a high incidence of type 2 diabetes and metabolic syndrome in this population [2, 3].

Aldosterone, a part of the renin-angiotensin system (RAS), acts on the kidney to increase re-absorption of ions and water. The overall effect is an increase in blood volume and, eventually, an increase in blood pressure. An increase in the plasma concentration of ACTH, Angiotensin III, Angiotensin II (Ang II) or potassium, which are

all in concordance with plasma sodium deficiencies, stimulate adrenal gland aldosterone synthesis [4, 5].

RAS is present in the human prostate and may be activated in BPH, possibly contributing to the pathophysiology of this disorder by several pathophysiological effects like enhancing local sympathetic tone and cell growth. In addition, Ang-II has been demonstrated to be a cytokine, especially acting as a growth factor. The functional role of RAS in the prostate, however, is not clear [6].

Large epidemiological studies warrant the association between vitamin D deficiency and BPH. The new focus of attention is the extent of involvement of vitamin D-related factors. A recent population-based study reported that serum calcium and parathyroid hormones stimulate prostate growth [6].

As is well known, aldosteronism, or chronic elevation in plasma aldosterone (ALDO; inappropriate for dietary Na⁺ intake), is accompanied by an adverse structural remodeling of the heart and vasculature. ALDO is now considered a cardiovascular risk factor (alongside obesity, diabetes, hypertension and hyperlipidemia). Also, Rutledge et al. have reported prostate vascular resistance in patients with BPH to have positive correlations with cardiovascular risk factors and prostate size [7]. Apparently, the overall impact is more than individual actions of the elements in concern, but a shift in the fair balance between.

A number of investigators have clarified that aldosterone collaborates in the remodeling of renal and cardiac tissue [8]. Although, particular clues presently point to it, the association between aldosteronism and prostatic tissue and prostate remodeling has not been widely recognized. We investigated the hypothesis that a relationship between chronic elevation in plasma aldosterone and lower levels of 25-hydroxy vitamin D(25-(OH)2D) in the prostate gland may be a feature of BPH.

Material and Methods

Our patient group was composed of 25 patients, suffering lower urinary tract disease symptoms suggesting benign prostate hyperplasia (median age 62 years, IQR (59.9–73.5)). Their physical examinations at the Urology Outpatient Clinic were also suggestive of their prediagnosis. Thirty volunteer healthy controls among the laboratory staff (median age 63.5 years, IQR (60–70)) without prominent urinary symptoms or history of urinary operations composed our control group.

The patients and controls were evaluated by the same urologist. All our subjects underwent a full,

detailed physical examination. We asked them to complete a general questionnaire. As a rule they all gave an informed consent. The questions included: age, social-economic status, origin of ancestors, status of physical activity, smoking, alcohol consumption and detailed medical history. We used a manual sphygmomanometer to measure blood pressure. After measuring the weight and height of the subjects, body mass index was calculated as weight (in kilograms) divided by height (in meters squared). We defined hypertension as ≥ 140 mm Hg systolic blood pressure and ≥ 90 mm Hg diastolic blood pressure.

Those with a known past history of any major diseases like hypertension, diabetes, cardiac disease, renal, hepatic or endocrine disease were excluded. None of the participants in the present study were using drug medications including anti-hypertensive and lipid lowering agents, vitamins or antioxidant drugs. Smokers and alcohol users were also excluded. The subjects were locals with average family income, strongly favoring common dietary habits, and routine daily life. Final diagnosis of each BPH patient was confirmed by a histopathological evaluation of prostate needle biopsies. This study was performed in accordance with the ethical standards set by the Helsinki Declaration and the local ethics committee approved it before onset.

Analytical Methods

Sample Collection

All samples were in an overnight fasting state at the time of blood sampling. Serum samples were immediately carried to the laboratory. Clear serum was separated from the cells by centrifugation (3000 rpm, 10 min). Serum total PSA, intact PTH, calcium and lipids (cholesterol, triglyceride, HDL and VLDL) levels were measured in fresh serum samples. We prepared multiple serum portions, stored them at -80°C refrigerator. Only after all the subjects were completed were the portions used to analyze 25-(OH) 2D and aldosterone.

The PTH and PSA kits used in our laboratory were methodically immunoenzymatic sandwich assays (Beckman Coulter, USA). Serum calcium levels and the lipid panel were determined by using commercially-available, ready-to-use assay kits (Abbott Diagnostics, USA). The LIAISON® 25 OH Vitamin D assay (DiaSorin) is a direct competitive chemiluminescence immunoassay.

Aldosterone was measured by means of a competitive enzyme immunoassay test (DRG® Aldosterone, EIA-4600) performed on Etimax micro elisa analyzer.

Statistical Analysis

We performed our statistical analyses using a computer program (MedCalc®, Belgium). As advised, the normally distributed group results are presented with means and all others with medians. We tested the significance of the differences between the two groups using a Student's unpaired t-test when groups showed normal distributions, and by using the Mann-Whitney *U*-test when they showed abnormal distributions. Still considering the distribution patterns, Pearson and Spearman correlation coefficients were used to test the strength of any associations. A *P* value ≤ 0.05 was accepted as the statistical significance level.

Results

The demographic data from the questionnaire and clinical findings of patients and controls are summarized in Table 1. The patients and controls were similar in age, and BMI. VLDL levels were significantly lower in BPH patients.

We evaluated associations between total PSA, total serum calcium, serum intact PTH, serum 25-(OH) D, and serum aldosterone levels in patients with BPH, compared to a non-BPH control group. We found serum aldosterone levels significantly higher in BPH patients ($p = 0.04$). BPH patients had significantly higher serum PSA levels ($p < 0.0001$). 25-(OH) 2D levels were lower in the BPH group ($p = 0.05$). Median 25-(OH) 2D levels in both groups were lower than the threshold reference limit (20 ng/mL). Serum PTH, and calcium levels were indifferent between the groups, and were within normal limits (Table 2).

Table 1. The patients and controls were similar in age and BMI. Lipid parameters showed no difference other than VLDL levels, which were significantly lower in BPH patients

Parameter (median-IQR)	BPH Patients (n = 25)	Controls (n = 30)	p
Age (years)	62 (59.9–73.5)	63.5 (60–70)	0.90
BMI (kg/m ²)	27 (24.2–29.7)	27.7 (25.9–28.7)	0.51
TC (mg/dL)	194 (167–237)	194 (177–221)	1.00
LDL-C (mg/dL)	127 (107–158)	119 (104–146)	0.38
HDL-C (mg/dL)	44 (36–54)	42 (35–47)	0.33
VLDL (mg/dL)	23 (16–36)	35 (23–42)	0.03

Table 2. Serum aldosterone and PSA levels were significantly higher, while 25-(OH)2D levels were lower in the BPH patient group compared to the control group

Parameter	BPH (25)	Controls (30)	Normal range	p
Aldosterone (pg/mL)	279 (185–694)	221 (172–256)	25–315	0.04
25-(OH)2D (ng/mL)	13.2 (7.3–20.4)	17.3 (11.7–22.4)	20–60	0.05
PTH (pg/mL)	39.4 (35.2–59.4)	42.6 (34.2–54.9)	15–88	0.55
Calcium (mg/dL)	9.7 (9.4–10.3)	9.7 (9.5–9.7)	8.2–10.9	0.49
PSA (ng/mL)	6.4 (5.4–8.9)	1.3 (0.9–1.7)	0.01–1	< 0.0001

Table 3. A complete list of optimal cut-off levels and associated diagnostics of 25-(OH)2D, PTH, aldosterone and calcium based on ROC analysis

Biomarker	Cut-off	Sensitivity (%)	Specificity (%)	AUC*	+LR [#]	–LR [#]
Aldosterone (pg/mL)	287.1	48	90	0.643	4.8	0.58
Calcium (mg/dL)	10	40	88.7	0.553	3	0.69
PTH (pg/mL)	27.7	92	23.3	0.546	1.2	0.34
25-(OH)2D (ng/mL)	8.2	36	96.7	0.644	10.8	0.66

*AUC – area under curve, [#] + and – likelihood ratio.

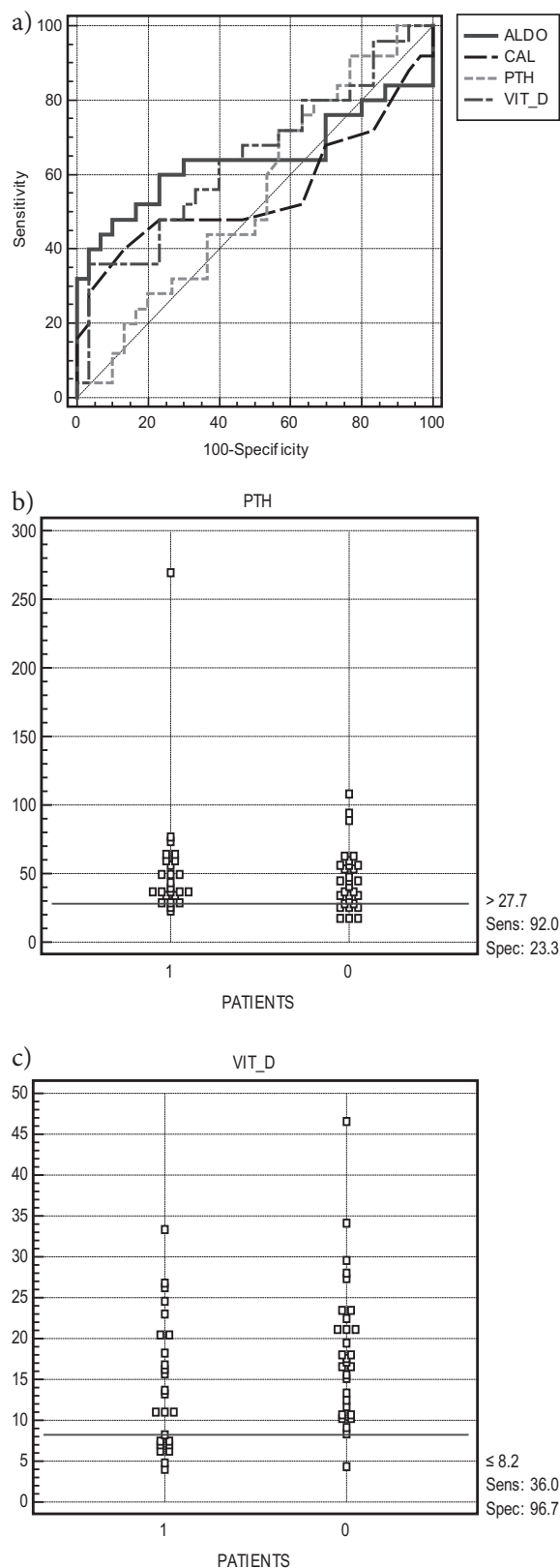


Fig. 1. PTH was superior in sensitivity whereas the other three were within close specificity percentages based on ROC analysis; a) ROC analysis of all 4 parameters, b) PTH, and c) 25-(OH)2D

Table 3 shows the ROC analysis, presenting optimal cut-off levels and associated diagnostic performances. 25-(OH) 2D showed a sensitivity

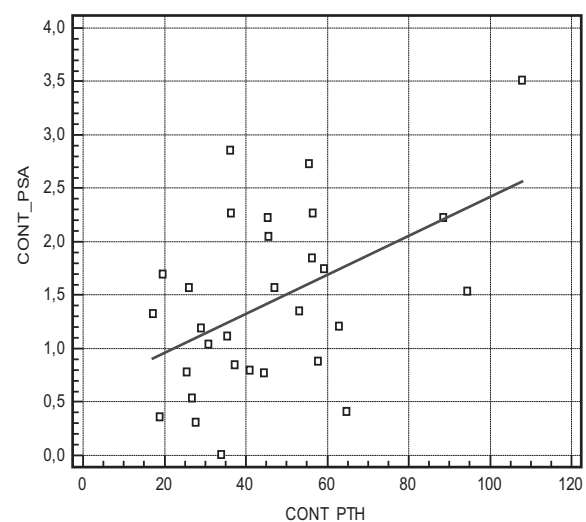


Fig. 2. There was a positive correlation between PTH and PSA levels in the control group ($p = 0.006$)

and specificity of 36% and 96.7%, respectively, and the area under curve (AUC) was 0.644. The diagnostic sensitivity and specificity of PTH were 92% and 23.3%, respectively, and the AUC was 0.546 (Fig. 1). The sensitivity, specificity and AUC for aldosterone were 48%, 90%, and 0.643. The sensitivity, specificity and AUC for calcium were 40%, 88.7% and 0.553. PTH was superior in sensitivity whereas the other three were within close specificity percentages.

A positive correlation was seen between PTH and PSA levels in the control group ($p = 0.006$) (Fig. 2).

Discussion

The most striking finding in this study was the higher aldosterone levels in patients with BPH. Our study may be the first to present the link between RAS and BPH. The vitamin D deficiency found in our BPH group was in line with previous studies. The co-existence of vitamin D deficiency and elevated levels of aldosterone composed the backbone of our assumptions [9].

Recent findings raise the possibility that aldosterone could influence a broad range of physiological and pathophysiological processes, such as intestinal calcium absorption, vascular inflammation and calcification, and blood pressure [10]. Of concern, aldosterone makes some of these happen through modifying the response of target tissues to 1,25-dihydroxy vitamin D(1,25(OH)2D) stimulation. Several 1,25(OH)2D target tissues, including intestinal epithelial cells and the cardiovascular system, have also been identified as sites of non-genomic aldosterone regulation [4, 11].

Vitamin D, as a versatile actor of the human metabolism, takes part in a wide variety of biological processes, including the immune response, insulin secretion, cardiovascular function and blood pressure, in addition to its very well-known role in calcium and phosphate homeostasis. To be an influencing factor in our study 1,25(OH)₂D has recently been identified as a regulator of the renin-angiotensin-aldosterone system (RAAS). It seems that aldosterone and 1,25(OH)₂D cooperate in the regulation of cell function and this interaction is very likely to be the result of cross talk between non-genomic and genomic steroid hormone signaling pathways [12, 13].

How vitamin D deficiency in patients might cause an overproduction of aldosterone was proposed to be through the activation of the RAAS axis. The mechanism of the inverse relationship between serum vitamin D levels and plasma renin hormone activity remained elusive until the study by Chopra et al. in which 1,25(OH)₂D was found to be a negative regulator of genetic renin expression [14]. The profit of this valuable finding was achieved by vitamin D analogues used in combination with angiotensin inhibitors. The patients taking combination therapy did not show the compensatory renin increase. The additive effect clearly increased the potential of these drugs. Sigmund has hypothesized in his paper that the cAMP signaling pathway was the target of 1,25-dihydroxy vitamin D, and through this, the vitamin functioned as a regulator of other renin stimulating factors that prevent the overproduction of renin [15]. In turn, hypocalcemia promotes secondary hyperparathyroidism with elevated circulating levels of PTH. Elevations in PTH lead to a rise in L-type Ca²⁺ channel entry and intracellular Ca²⁺ overloading involving diverse tissues, including the prostate [16–18]. There follows the induction of oxidative stress and ultimately necrosis of parenchymal cells with consequent tissue repair. Lost parenchyma and the appearance of reparative fibrosis each compromise organ function [19].

Collectively referred to as aldosteronism, this mineralocorticoid excess state is accompanied by ALDO-mediated classic responses that contribute to a heightened excretion of K⁺ and elevation

in arterial pressure, and frequently the retention of salt and water [7]. The putative risk factor for CVD, HT, shares the same characteristics of prevalence with BPH [1]. Although these two are separate disease processes, age-related increases in ALDO have been proposed to play a role in both of their pathophysiologies. McVary has extrapolated from statistical findings that if about 50% of men in their sixties have BPH and 50% of them have hypertension, then approximately 25% of men ≥ 60 years have BPH with co-morbid hypertension [1].

Aldosterone has also been linked to oxidative stress induction, which is the main path through multi-organ pathologies [19]. Recently, Calo et al. have reported in a human model that increased aldosterone production has effects on enzyme systems related to oxidative stress, enhancing the systemic fibrogenic effects of aldosterone excess through TGF-β and PAI-1 expression [20]. Studies have also demonstrated that Ang II induced oxidative stress, which was essential for vascular remodeling. Aldosterone was shown to induce fibrosis and remodeling through direct effect on some tissues [4, 5]. Another study showed that the drug Salinomycin induces aldosterone levels, which are known to act as oxidative stress inducers in prostate cells [21].

Serum calcium and parathyroid hormones are two actors shown to stimulate prostate growth. Although we could not determine an increase in PTH, the relationship between aldosterone, vitamin D and PTH should not be ignored. This calcitropic hormone is very probably involved in any process leading to cell death through intracellular Ca²⁺ overloading in diverse tissues, including prostate and their mitochondria, with an induction of oxidative stress [4, 5]. Yet one study showed that patients with histopathologically-proven BPH, high PTH, vitamin D, and calcium levels did not stimulate prostate growth [22, 23].

After all, the results of this study were derived from a small number of subjects, but still represent an important hypothesis for further research in a larger number of cases to clarify the role of aldosterone overproduction and its clinical relevance in human disease, particularly of the prostate [24, 25].

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