Parathyroid hormone is not involved in prostate growth in patients with benign prostatic hyperplasia

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The Master's Thesis
submitted to the Department of Medicine,
the Graduate School of Yonsei University
in partial fulfillment of the requirements for the degree
of Master of Medical Science

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June 2012

This certifies that the Master's Thesis of
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ACKNOWLEDGEMENTS

I would like to express my gratitude to all those who gave me the possibility to complete this thesis. I want to thank Prof. Dr. Yumie Rhee from the Department of Internal Medicine and Won Sik Ham from the Department of Urology, Yonsei University for giving me many advices for this thesis.

I am deeply indebted to my supervisor Prof. Dr. Young Deuk Choi from the Department of Urology, Yonsei University whose help, stimulating suggestions and encouragement helped me in all the time of research for and writing of this thesis. I also have furthermore to thank Prof. Dr. Wun Jae Kim and Prof. Dr. Seok Joong Yun, from the Department of Urology, Chungbuk National University who gave many suggestions to do the necessary research work and encouraged me to go ahead with my thesis in all the time of research.

15 April 2012
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ABSTRACT

Parathyroid hormone is not involved in prostate growth
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Purpose: A recent population-based study reported that serum calcium and parathyroid hormone stimulate prostate growth. We evaluated whether serum PTH, vitamin D, and calcium levels correlate with prostate size, PSA levels, and obesity in Korean patients with histologically proven BPH.

Methods: Patients with histopathologically proven BPH who underwent transurethral resection of the prostate were enrolled (n=289). Patients with PSA levels of ≥ 3 ng/ml underwent multicore transrectal prostate biopsy before TURP to rule out prostate cancer. Patients with serum creatinine levels >1.4 mg/dl, PSA levels >20 ng/ml, and/or PTH levels <10 pg/ml were excluded. Correlations between serum parameters and clinical data were determined. After adjustment for potential confounders, including age and body mass index, multiple linear regression served to compute associations.

Results: The mean age, serum PSA level, PTH level, and prostate size were 68.13±7.15 years, 4.10±3.88 ng/ml, 24.33±12.52 pg/ml, and 44.27±24.15 g, respectively. Prostate size correlated positively with age ($r=0.209$, $p<0.001$) and PSA levels ($r=0.481$, $p<0.001$), and PSA levels

correlated positively with age ($r=0.226$, $p<0.001$) and prostate size ($r=0.481$, $p<0.001$), but neither variable correlated with PTH, vitamin D, calcium levels, or BMI. Upon multiple adjusted linear regression analysis, prostate size correlated with BMI and serum PSA (both $p<0.001$), and serum PSA levels correlated with BMI and prostate size ($p=0.007$, $p<0.001$, respectively), but neither variable correlated with PTH, vitamin D, or serum calcium levels.

Conclusions: In Korean patients with histopathologically proven BPH, high PTH, vitamin D and calcium levels do not stimulate prostate growth.

Key words : Prostatic hyperplasia, Prostate, Parathyroid hormone

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I. INTRODUCTION

Benign prostatic hyperplasia is the most common disease of the prostate in aging men. The prevalence of BPH rises with age, with over 80% of men older than 80 years suffering from BPH[1]. Although the exact pathogenesis of BPH is not known, aging and testosterone levels are the most important factors for developing BPH[2]. In addition, religion, socioeconomic factors, sexual activity, alcohol intake, hypertension, and dietary factors are associated with BPH[3].

Prostate cells express the receptor for vitamin D[4] and Konety et al. have reported that vitamin D may play an important role in the growth and differentiation of the normal rat prostate as it has a growth-promoting effect on the prostatic stroma *in vivo*[5]. Moreover, treatment of castrated animals with vitamin D significantly enhances the growth and differentiation of the prostate, resulting in a prostate that is twice the size of the prostate of an untreated animal[5].

PTH is an 84-amino acid peptide hormone that is responsible for regulating the calcium and phosphate levels in the blood. It also regulates the serum levels of vitamin D. Therefore, PTH may influence normal prostate cells indirectly. A recent population-based study by Skinner and Schwartz hypothesized that serum calcium and PTH stimulate prostate growth in men since both serum

calcium and PTH levels correlated positively with free PSA levels[6]. This was the first report showing a relationship between PTH and PSA in men. However, it should be noted that this study involved serum tests performed in 1,273 men who were ≥ 40 years of age and who participated in the 2005–2006 United States National Health and Nutrition Survey and that objective data such as prostate size were not recorded. Moreover, since several lines of evidence suggest that the factors that promote BPH may vary considerably depending on ethnicity[7], it is not clear whether the observations of Skinner and Schwartz are also true for Asians. Since the relationship between PTH and prostate size in Asian men with histopathologically proven BPH has not yet been established, we evaluated the relationship between serum PTH, vitamin D and calcium levels, and clinical variables such as prostate size, PSA levels, and obesity in patients with histologically proven BPH.

II. MATERIALS AND METHODS

1. Patient characteristics

For the current study, the data of 346 patients who underwent TURP and were histologically confirmed to have BPH were reviewed retrospectively. In addition, to rule out prostate cancer, patients whose PSA levels were at least 3 ng/ml were subjected to multicore (mainly 12 cores) transrectal prostate biopsy before TURP. The Ethics Committee of Chungbuk National University approved this protocol. The collection and analysis of all samples was approved by the Institutional Review Board of Chungbuk National University. Prostate size was measured by transrectal ultrasound and the volume was calculated from transverse images by using the prolate-ellipse formula (0.524 x height x width x length)[8]. To rule out the possibility of including patients with chronic kidney disease or prostate cancer, patients whose creatinine levels exceeded 1.4 mg/dl or whose PSA levels were more than 20 ng/ml were excluded. Also excluded were patients whose serum PTH levels were less than 10 pg/ml, or who had parathyroid disease, osteoporosis, or any medications that affect PTH levels. In total, 289 patients with histopathologically proven BPH were enrolled.

2. Laboratory tests

On the morning of the day of operation, patient serum was taken and stored at -80℃ until use. Serum PSA levels were measured by using a quantified monoclonal IRMA radioimmunoassay (Izotop, Budapest, Hungary). PTH and Vitamin D levels were measured by using an Elecsys 2010 autoanalyzer (Roche Diagnostics, Indianapolis, IN) according to electrochemiluminescence immunoassay principles. Intact PTH levels were measured by a method that employs intact PTH-specific monoclonal antibodies and is based on the sandwich test principle. The vitamin D assay was based on the competitive test principle and employed a polyclonal vitamin D-specific antibody. All assays

were performed according to the manufacturer's instructions.

3. Statistical analysis

Correlations between prostate size and serum PSA, PTH, vitamin D, and calcium levels were assessed. In addition, the patients were separated into two groups on the basis of prostate size (<40 g or ≥40 g) or PSA levels (<4 ng/ml or ≥4 ng/ml) and their mean serum PTH, vitamin D and calcium levels were compared by using independent T-tests. Multiple linear regression analysis was performed to evaluate the association between prostate size and other parameters. Statistical analyses were performed by using the Statistical Package for Social Sciences, version 12.0, software (SPSS Inc., Chicago, IL). All tests were performed using a 2-tailed analysis and a p value < 0.05 was considered to be statistically significant.

III. RESULTS

1. Baseline characteristics

The mean age of the study population was 68.13±7.15 years and the mean BMI was 23.76±3.10 kg/m^2. The mean serum PSA level, PTH level, and prostate size were 4.10±3.88 ng/ml, 24.33±12.52 pg/ml and 44.27±24.15 g, respectively. Other baseline characteristics of the patients are presented in Table 1.

Table 1. Baseline characteristics of the patients with BPH

	Mean
Age (years)	68.13 ± 7.15
BMI (kg/m^2)	23.76 ± 3.10
PSA (ng/ml)	4.10 ± 3.88
Prostate size (g)	44.27 ± 24.15
Vitamin D (ng/ml)	18.64 ± 8.42
PTH (pg/ml)	24.33 ± 12.52
Calcium (mg/dl)	9.21 ± 0.54

BMI: body mass index

PSA: prostate-specific antigen

PTH: parathyroid hormone

2. Correlations between prostate size or PSA level and clinico-laboratory parameters

As shown in Table 2, prostate size correlated positively with age (r=0.209, p<0.001) and PSA levels (r=0.481, p<0.001) but not with BMI or PTH, vitamin D, or calcium levels. PSA levels correlated positively with age (r=0.226, p<0.001) and prostate size (r=0.481, p<0.001) but not BMI, or PTH, vitamin D or calcium levels.

Table 2. Correlations between prostate size or PSA levels and clinical and laboratory parameters

	Prostate size		PSA	
	correlation (r)	p-value	correlation (r)	p-value
Age (years)	0.209	<0.001	0.226	<0.001
BMI (kg/m^2)	0.133	0.053	-0.134	0.057
PTH (pg/ml)	0.028	0.636	0.038	0.515
Vitamin D (ng/ml)	-0.019	0.742	-0.044	0.456
Calcium (mg/dl)	0.018	0.763	0.001	0.996
Prostate size (g)	-	-	0.481	<0.001
PSA (ng/ml)	0.481	<0.001	-	-

BMI: body mass index

PTH: parathyroid hormone

PSA: prostate-specific antigen

3. Comparisons of clinical and laboratory parameters in BPH patients divided according to prostate size

As shown in Table 3, when the patients were divided into two groups according to prostate size (<40 g or ≥40g), the patients with bigger prostates were significantly older and had higher PSA levels than those with smaller prostates (p=0.001 and <0.001, respectively). However, the two groups did not differ significantly in terms of BMI or vitamin D, PTH, or calcium levels (p=0.069, 0.965, 0.317 and 0.509, respectively).

Table 3. Comparison of clinical and laboratory parameters in BPH patients after their division into two groups according to prostate size (<40 g and ≥40 g)

	Prostate size (<40 g) (n=147)	Prostate size (≥40 g) (n=142)	p-value
Age (years)	67.69 ± 7.44	70.40 ± 6.64	0.001
BMI (kg/m^2)	23.38 ± 3.21	24.16 ± 2.95	0.069
Total PSA (ng/ml)	2.70 ± 2.89	5.57 ± 4.13	<0.001
Prostate size (g)	26.45 ± 7.43	62.73 ± 21.44	<0.001
Vitamin D (ng/ml)	18.72 ± 8.46	18.67 ± 8.45	0.965
PTH (pg/ml)	23.68 ± 25.16	25.16 ± 13.61	0.317
Calcium (mg/dl)	9.20 ± 0.60	9.24 ± 0.48	0.509

BMI: body mass index

PSA: prostate-specific antigen

PTH: parathyroid hormone

4. Comparisons of clinical and laboratory parameters in BPH patients according to PSA

As shown in Table 4, when the patients were divided into two groups according to PSA levels (<4 ng/ml or ≥4 ng/ml), the patients with higher PSA levels were older and had larger prostates than those with lower PSA levels (both $p<0.001$). However, the two groups did not differ significantly in terms of BMI, or vitamin D, PTH or calcium levels (all $p>0.05$).

Table 4. Comparison of clinical and laboratory parameters in BPH patients after their division into two groups according to PSA levels (<4 and ≥4 ng/mL)

	PSA (<4) (n=188)	PSA (≥4) (n=101)	p-value
Age (years)	67.77 ± 7.01	71.36 ± 6.93	<0.001
BMI (Kg/m^2)	23.97 ± 3.11	23.31 ± 3.06	0.150
Total PSA (ng/ml)	1.79 ± 1.06	8.07 ± 3.59	<0.001
Prostate size (g)	36.76 ± 18.33	58.27 ± 27.33	<0.001
Vitamin D (ng/ml)	18.86 ± 8.86	18.38 ± 7.62	0.640
PTH (pg/ml)	24.18 ± 11.22	24.84 ± 14.89	0.672
Calcium (mg/dl)	9.21 ± 0.55	9.23 ± 0.53	0.750

BMI: body mass index

PSA: prostate-specific antigen

PTH: parathyroid hormone

5. Multiple linear regression analysis of the associations between prostate size or serum PSA concentration, and calcium, PTH and vitamin D levels

As shown in Table 5, in multiple adjusted linear regression analysis, prostate size associated significantly with BMI and serum PSA (both $p<0.001$), and serum PSA levels associated significantly with BMI and prostate size ($p=0.007$ and <0.001, respectively). However, neither prostate size nor PSA levels associated significantly with PTH, vitamin D, or calcium levels.

Table 5. Multiple linear regression analysis of the correlation between prostate size or serum PSA levels, and total calcium, PTH and vitamin D levels

	Estimate (β)	Standardized coefficients	p-value
Prostate size			
Age (years)	0.361	0.102	0.112
BMI (kg/m^2)	1.768	0.224	<0.001
PTH (pg/ml)	0.108	0.055	0.363
Vitamin D (ng/ml)	0.011	0.004	0.951
Calcium (mg/dl)	2.491	0.055	0.359
PSA (ng/ml)	3.624	0.554	<0.001
Serum PSA			
Age (years)	0.059	0.109	0.088
BMI (kg/m^2)	-0.206	-0.171	0.007
PTH (pg/ml)	-0.013	-0.044	0.468
Vitamin D (ng/ml)	-0.019	-0.043	0.479
Calcium (mg/dl)	0.217	0.032	0.600
Prostate size (g)	0.084	0.553	<0.001

BMI: body mass index

PTH: parathyroid hormone

PSA: prostate-specific antigen

IV. DISCUSSION

In this study, we could not find any evidence supporting the notion that PTH and calcium stimulate prostate growth in patients with pathologically proven BPH.

To date, many studies examining the roles vitamin D and PTH play in the developemt of prostate cancer[9-13]. Vitamin D has been shown to decrease the risk of prostate cancer[9-10]. In particular, it has been found that vitamin D has an antiproliferative effect on prostate cancer cell lines because it induces cell cycle arrest *via* the vitamin D receptor on the cancer cells[10]. However, PHT may play integral role in prostate cancer that results in the increased proliferation and migration of prostate cancer cells[13].

While an experimental animal study has shown that vitamin D is involved in the differentiation and organization of the normal prostate[5], little is known about the role PTH plays in normal prostate growth or BPH in humans. Recently, Skinner and Schwartz reported their population-based study of men ≥40 years of age who did not have clinical prostate cancer[6]. This study revealed that serum PTH and PSA, as well as calcium and free-PSA showed the positive correlation. However, our observations contradict these findings. These conflicting results might be due to several reasons. First, the study populations differed in terms of the subjects. The study of Skinner and Schwartz was a population-based study of men ≥40 years of age who participated in the 2005–2006 US National Health and Nutritional Examination Survey. In contrast, the present study only included patients with histologically proven BPH who underwent TURP due to severe obstructive symptoms, urinary retention or medication failure. This was why the mean PSA level (4.1 ng/ml) was higher than of normal general populations, and a limitation of the current study, namely that our subjects do not represent the general Korean population. Second, the study populations differed with regard to race. The subjects of the current study were all Korean. In contrast, while Skinner and Schwartz did not fully describe the ethnic makeup of their study

population, 10.5% were African Americans, with the remainder being American of undetermined ethnicity. It has been well established that ethnicity influences prostate size and PSA levels, perhaps because of variations in testosterone levels, dietary habits, and/or environmental factors[7]. In addition, it has been shown that Asian men have higher serum PSA levels per unit of prostate volume than Caucasian men, and there are well-established racial differences between Western and Eastern populations in terms of BPH[14-16]. Finally, the study by Skinner and Schwartz did not exclude the possibility that some of its 1,273 subjects had occult chronic kidney disease or indolent prostate cancer since prostate biopsies or TURP was not performed in subjects whose serological data were suggestive of possible prostate cancer. In contrast, in the current study, all patients with high PSA levels of ≥3 ng/ml or a palpable nodule in the digital rectal exam underwent prostate biopsy. This meant that the possibility of hidden prostate malignancy was almost excluded.

In the present study, multiple regression analysis revealed that BMI correlated positively with prostate size but negatively with serum PSA levels. Although there remains some controversy regarding this issue, it is now generally accepted that obese men have bigger prostates than non-obese men. Supporting this notion is the study of 68 men with BPH by Soygur et al., which found that the average prostate weight increased with age and BMI[17]. In addition, Daniell has found upon examining the prostatectomy specimens of 379 men that obese men have larger adenomas[18]. Specifically, it was found that the group of underweight men, when compared to men who were at least 30% overweight, had more small specimens (10 g or less, 24% *vs.* 2%, $p<0.001$) and fewer large specimens (50 g or more, 5% *vs.* 26%, $p<0.005$). It is also apparent that obese men have lower serum PSA levels than men with normal weights[19-21]. This may be because obese men have decreased circulating levels of androgens and/or their PSA levels are subjected to an obesity-related hemodilution effect. Thus, the results of the present study correspond well with those of earlier

studies.

In summary, this study is the first to examine the relationship between serum PTH and vitamin D levels with PSA levels and prostate size in BPH patients. We found that neither prostate size nor PSA levels correlate with PTH or vitamin D levels.

V. CONCLUSION

In patients with histopathologically proven BPH, prostate size and PSA levels correlated with BMI, but not with PTH, vitamin D or calcium levels. This contradicts the observations of a population-based study of American men. However, it remains possible that the relationship between PTH and prostate size in the general American male population differs from that in Korean BPH patients. Consequently, further studies examining the relationship between PTH and prostate growth in different races are needed, along with a population-based study on Asian men.

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ABSTRACT(IN KOREAN)

전립선비대증 환자에서 부갑상선호르몬은 전립선의 성장에 관여하지 않는다

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김 원 태

목적: 최근 임상적으로 전립선암이 없는 전립선비대증 환자에서 혈중 칼슘과 부갑상선호르몬 (PTH)이 PSA 와 상관관계가 있어 PTH 가 전립선의 성장을 촉진시킬수 있다는 가설이 보고되었다. 저자들은 병리적으로 확진된 한국인 전립선비대증 환자에서 혈중 부갑상선호르몬, vitamin D, 칼슘양과 전립선 크기, PSA, 비만의 상관관계를 분석하였다.

대상 및 방법: 경요도전립선절제술을 시행받아 전립선비대증으로 확진된 환자 중에서 만성신질환을 배제하기 위해 Cr 1.4 mg/dl 이상, 전립선암을 배제하기 위해 PSA 20 ng/ml 이상, 갑상선 및 부갑상선 질환을 배제하기 위해 PTH 10pg/ml 이하인 환자는 제외하고 총 289 명의 환자를 분석하였다. PSA 가 4 ng/ml 이상인 환자는 전립선생검을 시행하여 전립선암이 없는 환자만을 연구에 포함시켰다. 혈중 PTH, vitamin D, PSA, 혈중칼슘양, 전립선크기, 체질량, 나이 등을 분석하였다. 혈중 인자와 임상자료의 상관관계를 분석하였고, 나이, 체질량지수를 포함한 혼란변수를 보정후 다중선형회귀분석을 실시하여 연관성을 분석하였다.

결과: 환자의 평균나이는 68.13 ± 7.15 세였고, 평균 PSA 는 4.10 ± 3.88 ng/ml, 평균 전립선크기는 44.27 ± 24.15g, 평균 혈중 PTH 는 24.33 ± 12.52 pg/ml 였다. 전립선 크기는 나이, PSA 와 양의 상관관계를 보였고 ($r=0.209$, $p<0.001$; $r=0.481$, $p<0.001$, respectively), PSA 역시 나이, 전립선크기와 양의 상관관계를 보였다 ($r=0.226$, $p<0.001$; $r=0.481$, $p<0.001$, respectively). 다중선형회귀분석에서 전립선크기는 체질량과 PSA 와 연관이 있었고 (both, $p<0.001$), 혈중 PSA 역시 체질량과 전립선크기와 연관이 있었다 ($p=0.007$, $p<0.001$, respectively). 그러나, 전립선 크기와 PSA 는 혈중 PTH, vit D3, 혈중 칼슘양과 연관이 없었다.

결론: 병리학적으로 확진된 한국인 전립선비대증환자에서 높은 혈청 부갑상선호르몬, vitamin D, 칼슘은 전립선의 크기를 증가시키지 않는다.

핵심되는 말 : 전립선비대증, 부갑상선 호르몬, 전립선특이항원