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Özgün araştırma / Original research

Yaşlanan Erkekte Benign Prostat Hiperplazisine Bağlı Alt Üriner Sistem Semptomları ile Vitamin D Seviyesi Arasındaki İlişki

The Relationship Between Benign Prostate Hyperplasia Related Lower Urinary Tract Symptoms And Vitamin D Level in Aging Male

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Özet

Amaç: 40 yaşın üzerindeki erkeklerde vitamin D düzeyleri ile benign prostat hiperplazisi (BPH) ne bağlı alt üriner sistem semptomları (AÜSS) arasındaki ilişkiyi belirlemeyi amaçladık.

Gereç Ve Yöntemler: Çalışmamıza Ocak 2019-Nisan 2019 tarihleri arasında kliniğimize BPH'ya bağlı AÜSS ile başvuran 48 hasta (BPH grubu) ile AÜSS olmayan ve rutin ürolojik kontrole gelen 52 hasta (Kontrol grubu) dahil edildi. Her iki grubun vitamin D, total PSA, total testosteron değerleri, IPSS skorları, prostat hacimleri ve üroflowmetrideki maksimum idrar hızı (Qmax) değerlendirildi.

Bulgular: BPH grubundaki 48 hastanın yaş ortalaması 65,37 ± 7,24, kontrol grubundaki 52 hastanın yaş ortalaması 64,09 ± 8,22 idi. BPH ve kontrol grupları arasında 25 hidroksi vitamin D değerlerinin ortalama değerleri açısından istatistiksel olarak anlamlı bir fark vardı (p <0.001). BPH grubundaki hastalar alt gruplarına göre incelendiğinde; Orta AÜSS (33 hasta) ve şiddetli AÜSS (15 hasta) grubu arasında 25 hidroksi vitamin D düzeyi açısından istatistiksel olarak anlamlı fark yoktu (p> 0.05).

Sonuç: Çalışmamız BPH ve AÜSS olan hastalarda 25 hidroksi vitamin-D düzeylerinin şikayeti olmayan benzer yaş grubundakilerden düşük olduğunu göstermiştir. Buna dayanarak, vitamin D düzeylerinde artış olan hastaların semptomlarında bir iyileşme olabileceği düşünülmektedir. Bu konuda kesin bir karara varmak için, daha fazla sayıda randomize kontrollü prospektif çalışmaya ihtiyaç vardır.

Anahtar Kelimeler: Vitamin D, benign prostat hiperplazisi, alt üriner sistem semptomları

Abstract

Objective: We aimed to determine the relationship between vitamin D levels and benign prostate hyperplasia (BPH) related lower urinary tract symptoms (LUTS) in men over 40 years of age.

Material and Methods: The study was conducted prospectively between January and April 2019 and included 48 patients who presented to the outpatient clinic with lower urinary tract symptoms and who had not received medical or surgical treatment due to BPH (BPH group) and 52 healthy men (Control group) who did not have lower urinary tract symptoms and applied to the outpatient clinic for routine urological control. Vitamin D, total PSA, total testosterone values, IPSS scores, prostate volumes and maximum urinary velocity in uroflowmetry (Q max) of both groups were evaluated.

Results: The mean age of 48 patients with benign prostatic hyperplasia in BPH group was 65.37 ± 7.24 and in control group without urinary tract symptoms was 64.09 ± 8.22. There was a statistically significant difference between BPH and control groups in terms of the mean values of 25 hydroxy vitamin-D values (p< 0.001). When the patients diagnosed with BPH were examined according to their subgroups; there was no statistically significant difference in terms of 25 hydroxy vitamin D levels between moderate LUTS (33 patients) and severe LUTS (15 patients) groups(p> 0.05).

Conclusion: Our study has shown that in patients with BPH and LUTS, 25 hydroxy vitamin D levels were lower than those in the similar age group without any complaints. Based on this, it was thought that there might be an improvement in the symptoms of patients with increasing vitamin D levels. To reach a final judgment on this subject, larger number of randomized controlled prospective studies are needed.

Keywords: Vitamin D, benign prostate hyperplasia, lower urinary tract symptoms

INTRODUCTION

Lower urinary tract symptoms are divided into three groups as voiding, storage and post-micturition symptoms (1). Lower urinary tract symptoms have a direct relationship with aging (2). Benign prostatic hyperplasia (BPH) is one of the most common causes of lower urinary tract symptoms (LUTS) in aging men. Traditionally, voiding symptoms are thought to be due to bladder outlet obstruction (3). The etiology of BPH is multifactorial. Although many studies have been conducted on the etiology of prostatic growth in recent years, nowadays the cause and effect relationship has not been established clearly. Voiding symptoms show a low correlation with underlying pathophysiology (4). The role of androgens and androgen receptors in the development of BPH remains unclear. On the other hand, although the role of estrogens in animal experiments is shown, the effect on development of BPH has not been demonstrated. It was thought that the relationship between growth hormones and steroids may play a role in the development of BPH (5). There are studies showing that vitamin D3 deficiency may play a role in many diseases and metabolic function of many organs in recent years (6, 7, 8). The prevalence of vitamin D deficiency in the male urological population may indicate a link between BPH and vitamin D. Studies on the physiology of the lower urinary tract suggest that vitamin D receptors may play a role in the treatment of lower urinary tract symptoms in the future (9,10). There are studies suggesting that vitamin D treatment may reduce prostate size and BPH prevalence (11, 12). In addition, it was shown that vitamin D agonist inhibits smooth muscle contraction and proliferation in the bladder and prostate (13, 14). On the other hand, a placebo-controlled phase 2 study showed that vitamin D agonist significantly decreased prostate volume but did not significantly increase uroflowmetric parameters (11). In this case control study, we aimed to determine the relationship between vitamin D levels and lower urinary tract symptoms in men over 40 years of age.

MATERIAL AND METHODS

Our study was conducted prospectively between January 2019 and April 2019. Written informed consent was obtained from all patients. The study included 48 patients who presented to the outpatient clinic with lower urinary tract symptoms and who had not received medical or surgical treatment due to BPH (BPH group) and 52 men (Control group) who did not have lower urinary tract symptoms and applied to the outpatient clinic for psa screening without lower urinary tract symptoms, routine renal cortical cyst control or symptoms other than lower urinary tract symptoms like loin pain. Vitamin D, total PSA, total testosterone values, International Prostate Symptom Score (IPSS), prostate volumes and maximum urinary velocity in uroflowmetry (Q max) of both groups were evaluated. Serum 25 (OH) vitamin D levels were measured to evaluate vitamin D status. Patients were classified according to IPSS scores as follows; 0: none, 1-7: mild, 8-19: moderate, 20-35: severe. Prostate volumes of the patients were evaluated by urinary system ultrasound. Patients under the age of 40 years, with acute urinary tract infection, neurogenic bladder, urethral stricture, chronic pelvic pain syndrome, bladder tumor and had diabetes, chronic neurological, cardiovascular disease, and who received vitamin D treatment or who had medications to affect the serum vitamin D level were excluded from the study. In addition, patients with total PSA> 2.5 ng / ml or with suspicious nodal examination were excluded from the study.

Statistical Analysis

While evaluating the findings obtained in the study, IBM SPSS Statistics 22 program was used for statistical analysis. In the evaluation of study data, normal distribution of parameters was evaluated by Kolmogorov- Smirnov and Shapiro Wilks test. Student's t- test was used for normal distrubution of numeric variables. Mann- Whitney- U test was used for abnormal distribution variables. Significance was evaluated as $p < 0.05$.

RESULTS

The study was carried out between January 2019 and April 2019 with a total of 100 patients whose ages ranged from 44 to 77 years. The mean age of 48 patients with benign prostatic hyperplasia in BPH group was 65.37 ± 7.24 years and in control group without

urinary tract symptoms was 64.09 ± 8.22 years. According to the results of the study, there was no statistically significant difference in terms of mean age of the patients who were diagnosed as BPH and were determined as control group (p> 0.05). There was no statistically significant difference between the serum PSA and total testosterone levels of the patients with BPH and the control group (p> 0.05). When the patients were evaluated in terms of the Qmax in uroflowmetry, the mean Qmax of the patients in the BPH group was statistically lower than in the control group (p< 0.001). When the ultrasound-calculated prostate volumes were evaluated; the mean prostate volumes of the BPH group were significantly higher than the control group (p< 0.001). Also there was statistically significant difference between groups in terms of IPSS (p< 0.001). On the other hand there was a statistically significant difference between BPH and control groups in terms of the mean values of 25 hydroxy vitamin D (p< 0.001) (Table 1). When the patients diagnosed with BPH were examined according to their subgroups; there was no statistically significant difference in terms of 25 hydroxy vitamin D level between moderate LUTS (33 patients) and severe LUTS (15 patients) groups (p> 0.05) (Table 2).

Table 1: Comparison of values assessed in the study between BPH and control groups

	BPH (N=48) Median (min-max) Mean (± SD)	**Control (N=52)** Median (min-max) Mean (± SD)	**P**
Age (years)	65.37 (7.24)	64.09 (8.22)	0,41
Total PSA (ng/ml)	1.53(0.28-2.50)	1.25 (0.26-2.40)	0.080
IPSS	16.5 (8-27)	2 (0-4)	<0.001*
Prostate volume (cc)	48.5 (22-109)	30 (20-64)	<0.001*
TT (ng/ml)	4.69 (2.21-9.57)	5.07 (0.34-13.2)	0.692
Qmax (ml/s)	12 (8.7-15)	16.9 (13.9-24)	<0.001*
25 hydroxy vitamin D (ng/mL)	14.4 (4.2-64.3)	19.2 (10.40-29.90)	<0.001*

*Mann Whitney U test *p<0.05*
BPH: Benign prostate hyperplasia
IPSS: International Prostate Symptom Score
TT: Total Testosteron

Table 2: Comparison of subgroups of patients with benign prostatic hyperplasia according to IPSS score

	Moderate LUTS (N=33) Median (min-max)	**Severe LUTS (N=15)** Median (min-max)	**P**
Age (years)	64 (50-79)	68 (56-80)	0,255
Total PSA (ng/ml)	1.39 (0.28-2.50)	2.20 (0.67-2.50)	0.084
Prostate volume (cc)	43 (22-109)	57 (38-80)	0.010*
TT (ng/ml)	4.94 (2.21-9.57)	4,37 (2.21-6.93)	0.023*
Qmax (ml/s)	13 (11-15)	10 (8.7-11)	<0.001*
25 hydroxy vitamin D (ng/mL)	15.2 (4.2-64.3)	12.1 (7.8-17.30)	0.100

*Mann Whitney U test *p<0.05*
TT: Total Testosteron
LUTS: Lower urinary tract symptoms

DISCUSSION

Bladder outlet obstruction due to benign prostatic hyperplasia is one of the most common causes of lower urinary tract symptoms. Lower urinary tract symptoms over the age of 60 reach 70% and are thought to be an important health problem affecting quality of life (15).

The etiology and pathophysiology of the lower urinary tract symptoms related to BPH have not been elucidated in clinical and experimental studies to date. Androgen and estrogen receptors, growth factors and genetic factors may play a role in the pathophysiology of BPH. On the other hand, in recent years, vitamin D receptors are thought to play a role in pathophysiology. Vitamin D receptors are found in the bladder and prostate (9). The prostate gland plays a role in the endocrine and autocrine pathways of vitamin D metabolism and can convert 25 hydroxy vitamin D into the active form of 1.25 hydroxy vitamin D (10). Experimental studies on the effect of Vitamin D receptor agonist, BXL628 (elocalcitol), on BPH showed promising results. Consequent clinical studies on Vitamin D analog proved that it prevents the proliferation of bladder and prostatic smooth muscle cells in BPH, which is thought to be through inhibition of the RhoA/Rho kinase pathway (14). Also observational studies have shown that the intake of both dietary and supplemental vitamin are inversely associated with BPH prevalence (16). Actually elocalcitol, a vitamin D analogue, has an inhibitory effect on the in vitro proliferation of patient-derived benign prostatic stromal cells and PCa epithelial cells (17).

Although the relationship between prostate cancer and vitamin D deficiency has been shown in many epidemiological studies, the study evaluating the relationship between vitamin D deficiency and lower urinary tract symptoms is less in the literature (17,18). Elshazly et al. Found statistically significant difference in terms of vitamin D levels between the patients with lower urinary tract symptoms and control group (40.82 ± 29.46 nmol / L vs. 70.25 ± 22.42 nmol /) ($p < 0.001$). However, in this study, there was no statistically significant correlation between IPSS and vitamin D levels in Pearson correlation analysis ($r = 0.07$) (19). In the same study, there was no correlation between prostate volume, PSA, calcium and vitamin D levels. In a large population study conducted by Vaughan et al., 2387 men were evaluated for vitamin D levels and lower urinary tract symptoms, and vitamin D levels were found to be <30 ng / dl in 1241 men and <20 ng / dl in 684 patients. At least one lower urinary tract symptom was detected in 666 patients, and vitamin D deficiency was associated with at least one lower urinary tract symptom (POR 1.4, 95% CI 1.0, 2.0) (20). This study in the United States is the largest population study in the literature evaluating the relationship between vitamin D level and lower urinary tract symptoms. The study evaluating this relationship in other geographic places is not available in the literature. On the other hand, clinical studies have been conducted to evaluate the effect of metabolic syndrome on the relationship between vitamin D level and lower urinary tract symptoms. Park et al. evaluated the effect of metabolic syndrome on the relationship between vitamin D level and lower urinary tract symptoms and found that vitamin D level positively correlated with total testosterone level in patients without metabolic syndrome and negatively correlated with IPSS and prostate volume (21). In the study conducted by Caretta et al., the relation between vitamin D deficiency and lower urinary tract symptoms in type 2 diabetes mellitus (DM) patients was evaluated and it was observed that 25 OH vitamin D levels decreased progressively with increasing IPSS scores in type 2 DM patients. The correlation between 25 OH vitamin D levels and IPSS remained statistically significant after correction of age, body mass index, PSA and testosterone ($R = -0.305$, $p = 0.020$) (22). In our study, 25 hydroxy vitamin D levels of patients diagnosed with BPH were found to be significantly lower than the control group. When BPH patients were divided into subgroups according to their symptom severity (moderate vs severe LUTS); there was no statistically significant difference in terms of 25 hydroxy vitamin D levels.

Our study has some limitations. Vitamin D levels of patients were evaluated only once, so they may not fully reflect the long-term vitamin D status. This is important for a disease with long-term progression such as BPH. On the other hand, although the known DM patients were excluded from the study, the body mass index, waist circumference, total cholesterol, HDL cholesterol, diastolic and systolic blood pressures reflecting the status of patients with metabolic syndrome were not evaluated. Therefore, their effects on lower urinary symptoms and vitamin D

could not be evaluated. Lastly our study can not reflect status of vitamin D levels of our population because of small sample size.

CONCLUSION

Our study has shown that in patients with BPH related lower urinary tract symptoms, 25 hydroxy vitamin D levels were lower than those in the similar age group without any complaints. Based on this, it was thought that there might be an improvement in the symptoms of patients with increasing vitamin D levels. To reach a final judgment on this subject, larger number of randomized controlled prospective studies are needed.

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