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ORIGINAL ARTICLE

Cholecalciferol for the prophylaxis against recurrent urinary tract infection among patients with benign prostatic hyperplasia: a randomized, comparative study

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Abstract

Purpose To explore the role of cholecalciferol for the prophylaxis against recurrent urinary tract infection (UTI) in patients with benign prostatic hyperplasia (BPH).

Methods Our randomized, uncontrolled prospective study included 389 naïve BPH patients with moderate/severe symptoms, consecutively. The patients were randomly allocated to two groups; group-A included 193 patients who received tamsulosin, while group-B included another 196 patients who received tamsulosin with cholecalciferol. The study population was followed up for 2 years after the start of the treatment. For all the patients enrolled, clinical evaluation, imaging studies (abdominal and trans-rectal ultrasonography), and laboratory investigations [including urinalysis, urine culture with antibiotic susceptibility testing for positive cultures and estimation of prostate-specific antigen (PSA) level] were provided.

Results The incidence rate of recurrent UTI was 9% among the study population; it was significantly higher among group-A patients compared to those of group-B (13.5% vs. 4.6%, p 0.003, OR 2.7, 95% CI 1.5–4.3). Compared to patients of group-A, those of group-B developed a significantly lower level of PSA at the end of treatment period (0.16 ± 0.03 ng/mL vs. 0.27 ± 0.08 ng/mL, p 0.043, OR 1.9, 95% CI 1.2–6.8).

Conclusions Adjuvant cholecalciferol supplementation may be protective against recurrent UTI among patients with BPH receiving tamsulosin therapy without extra adverse effects.

Keywords Cholecalciferol · Urinary tract infection · Tamsulosin · Benign prostatic hyperplasia

Abbreviations

BPH	Benign prostatic hyperplasia
UTI	Urinary tract infection
AUA-SI	American Urological Association Symptom Index
PSA	Prostate-specific antigen
PVR	Post-void residue

Introduction

With aging, men acquire urinary tract abnormalities impairing normal voiding; the most common one is benign prostatic hyperplasia (BPH) [1], which is considered as one of the most common diseases of the elderly, affecting 50% of men aged 50–60 years [2]. In men, the incidence of urinary tract infection (UTI) increases with age from 0.9 to 2.4 cases per 1000 among men younger than 55 years to 7.7 cases per 1000 in those older than 85 years. One of the most

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frequent complications of BPH is recurrent UTI caused by the bladder outflow obstruction with subsequent infection of the residual urine. Intra-prostatic reflux of infected urine leads to the chronic existence of bacteria within the prostate and the urinary tract [3]. Among the patients with BPH, UTI prevalence is 15% [4]. Among the general population, the prevalence of vitamin D deficiency is 20–100% [5]; the rate of vitamin D deficiency can be higher among the elderly subjects—who are more vulnerable to BPH—due to their limited mobility and less exposure to sunlight.

The active form of vitamin D binds to the nuclear vitamin D receptors located in tissues including the immune cells [6]; it regulates transcription of the genes including those for antimicrobial peptides and cytokines [7]. Vitamin D deficiency was observed to be associated with infectious diseases like tuberculosis, respiratory tract infections, influenza, and sepsis [8]; however, the use of vitamin D supplementation for treatment and/or prevention of infections has not been proved [9].

The aim of our study is to explore the role of cholecalciferol (vitamin D_3) in the prophylaxis against recurrent UTI among the patients with BPH based on the hypothesis that vitamin D enhances the immune response keeping in consideration that this is the first study to investigate the role of vitamin D in preventing recurrent UTI among the patients with BPH. The elderly patients who have higher rates of BPH are expected to suffer more than the younger subjects from vitamin D deficiency; the coexistence of both conditions is not uncommon among such a population. We lack studies investigating the impact of vitamin D supplementation on prevention of UTI secondary to BPH.

Materials and methods

A hospital-based, prospective, randomized, comparative study was performed between March 2014 and May 2017 after approval of our institutional ethics committee and obtaining an informed consent from all participants. The study sample was recruited from patients attending the outpatient clinics or admitted to the inpatient sectors of the Department of Urology, the Department of Internal Medicine (Nephrology Unit), and the Department of Tropical Medicine (Infectious Diseases Unit).

Our study included 400 naïve BPH patients with moderate/severe symptoms [American Urological Association Symptom Index (AUA-SI) score > 7], consecutively. The patients were randomly (using block randomization method by Stata, version 13.1, StataCorp, for Microsoft Windows®) allocated to two groups; group-A included 200 patients who received tamsulosin (0.4 mg/day), while group-B included another 200 patients who received tamsulosin with cholecalciferol (600 IU/day, orally, immediately after lunch). Cholecalciferol was provided by Medical Union Pharmaceuticals (Vidrop®).

The treatment experienced patients for BPH, patients with PSA level of 0.4 ng/mL or more, pretreatment pyuria and/or hematuria, refractory urinary retention, urolithiasis, urinary bladder diverticula, previous urological surgery and renal insufficiency were excluded from being enrolled. In addition, patients with diabetes mellitus, glucose intolerance, neoplastic diseases during the previous 5 years, leukopenia, congestive heart failure, and hypercalcemia, and those receiving systemic corticosteroids, immune suppressant medications, antineoplastic chemotherapy, alternative and complementary medications for UTI and medications with potential contribution to lower urinary symptoms (antihistamines, decongestants, diuretics, opiates, and tricyclic antidepressants) were also excluded.

For all the enrolled patients, clinical evaluation (medical history and physical examination including estimation of AUA-SI score, digital rectal examination and estimation of the body mass index), imaging studies (abdominal and trans-rectal US) and laboratory investigations [urinalysis, urine culture on blood agar with antibiotic susceptibility testing for positive cultures, estimation of the serum levels of prostate-specific antigen (PSA), creatinine, and calcium level estimation, fasting serum level of glucose determination, and complete blood count] were provided.

The study population was followed up for 2 years after the start of treatment. During this period, monthly clinical and laboratory evaluation was carried out. The laboratory evaluation included urinalysis and urine culture for bacteria for all patients. Recurrent UTI was diagnosed based on two episodes of UTI with two positive urine cultures during a period of 6 months [10]. Patients who developed UTI received antibiotic therapy according to the results of antibiotic susceptibility testing and the clinical pattern of infection. At the end of follow-up period, the serum levels of PSA were re-estimated.

Data were analyzed using the Statistical Package for Social Sciences (IBM SPSS Statistics, version 22.0, release 22.0.0.0; IBM Corp.) for Microsoft Windows® (64-bit version). Results were expressed as mean ± standard deviation or frequency (percentage) as appropriate. Student's *t* test or Mann–Whitney *U* test, and Yates' corrected Chi-squared test or Fischer's exact test as appropriate were used to compare the variables between the study groups. A *p* value less than 0.05 was considered statistically significant.

Power analysis of the performed Chi-square tests was done using the G*power software version 3.1.9.2. A power of 85% was achieved to detect a medium sized effect. Plotting power against various effect size values showed reasonable power values for medium and large effect sizes. However, for detection of small effect size, the test appeared to be underpowered.

Results

Out of the study population (400 naïve BPH patients with moderate/severe symptoms), 11 were excluded during the study period; seven due to development of persistent urolithiasis (four in group-A and three in group-B), three due to development of refractory urinary retention (all in group-A) and one due to administration of systemic corticosteroids (group-B). After excluding the previously mentioned cases, the study population consisted of 389 patients (193 in group-A and 196 in group-B). Their mean age ± standard deviation was 64.3 ± 7.5 years.

The pretreatment demographic, clinical, imaging, and laboratory characteristics of the study population with BPH are shown in Table 1. When comparing the study groups regarding such characteristics, both were matching with no statistically significant difference between the patients of group-A and group-B.

Table 2 shows that 9% of the study population developed recurrent UTI that was significantly higher among group-A patients compared to those of group-B (13.5% vs. 4.6%, $p = 0.003$, OR 2.7, 95% CI 1.5–4.3). In addition, the incidence rate of solitary UTI was higher among group-A patients compared to those of group-B (18.7% vs. 11.7%, $p = 0.062$, OR 1.4, 95% CI 0.83–7.41), although it was not statistically significant.

Compared to patients of group-A, those of group-B had significantly more decrease of post-void residual (PVR) urine volume after treatment compared to before treatment

Table 1 Pretreatment demographic, clinical, imaging, and laboratory characteristics of the study population with BPH

	Group-A ($n = 193$)	Group-B ($n = 196$)	Total ($n = 389$)	p value
Age (years)	66.7 ± 5.2	61.9 ± 8.4	64.3 ± 7.5	0.097
Caffeine consumption	193 (100)	188 (95.9)	381 (97.9)	0.371
Tobacco smoking	117 (60.6)	132 (67.3)	249 (64)	0.263
BMI	30.2 ± 2.1	26.9 ± 4.6	28.7 ± 3.4	0.194
Systemic hypertension	71 (36.8)	64 (32.7)	135 (34.7)	0.206
AUA-SI	21 ± 5.2	17 ± 2.3	18 ± 3.6	0.179
Prostatic volume (cm^3)	55.4 ± 13.1	60.2 ± 10.8	57.9 ± 12.4	0.297
PVR urine volume	97 ± 18.3	133 ± 31.4	114 ± 27	0.059
PSA (ng/mL)	0.26 ± 0.09	0.19 ± 0.05	0.23 ± 0.07	0.167
Serum creatinine level (μmol/L)	89.4 ± 13.1	97.5 ± 9.9	93.8 ± 11.3	0.301
Fasting serum glucose level (mmol/L)	5.5 ± 0.3	4.9 ± 0.5	5.1 ± 0.6	0.485
Serum calcium level (mg/dL)	8.9 ± 0.6	9.4 ± 0.3	9.2 ± 0.4	0.513
WBC count ($\times 10^3/\mu L$)	5.7 ± 1.5	7.3 ± 0.9	6.8 ± 1.1	0.118
Hemoglobin level (g/dL)	11.9 ± 2.3	13.2 ± 2.1	12.7 ± 1.9	0.294
Platelets count ($\times 10^3/\mu L$)	293 ± 36.2	229 ± 40.5	261 ± 27.4	0.078

Table 2 Therapeutic outcome among the study population with BPH

	Group-A ($n = 193$)	Group-B ($n = 196$)	Total ($n = 389$)	p value
Solitary UTI	36 (18.7)	23 (11.7)	59 (15.2)	0.062
Recurrent UTI	26 (13.5)	9 (4.6)	35 (9)	0.003*
AUA-SI	18 ± 3.6	11 ± 4.2	14 ± 5.1	0.056
Change of AUA-SI[a]	3 ± 2.4	5.6 ± 2.1	4 ± 1.7	0.058
Prostatic volume (cm^3)	58.5 ± 9.9	55.1 ± 12.8	56.2 ± 10.7	0.338
Change of prostatic volume	3.3 ± 3.5	4.9 ± 2.2	1.9 ± 1.6	0.098
PVR urine volume (cm^3)	93 ± 12.7	88.3 ± 19.3	89.5 ± 15.1	0.206
Change of PVR urine volume	3.8 ± 0.6	44.9 ± 13.1	24.3 ± 12	< 0.001**
PSA level (ng/mL)	0.27 ± 0.08	0.16 ± 0.03	0.22 ± 0.06	0.043**
Change of PSA level	0.01 ± 0.009	0.032 ± 0.022	0.01 ± 0.011	0.052
WBC count ($\times 10^3/\mu L$)	5.1 ± 1.2	8.6 ± 1.4	6.9 ± 0.9	0.071
Tamsulosin-related adverse effects	5 (26)	6 (3.1)	11 (2.8)	0.627

*Statistically significant using Chi-square test

**Statistically significant using Student's t test

[a]Change after treatment compared to before treatment

(44.9 ± 13.1 vs. 3.8 ± 0.6 cm^3, $p < 0.001$), although the PVR volume was not significantly different between the patients of both groups regarding its post-treatment value. In addition, patients of group-B developed significantly lower levels of PSA at the end of treatment period compared to those of group-A (0.16 ± 0.03 ng/mL vs. 0.27 ± 0.08 ng/mL, p 0.043, OR 1.9, 95% CI 1.2–6.8). However, the change of PSA level before and after treatment was not significantly different between both groups. In spite of the development of less severe BPH parameters (lower AUA-SI score, smaller prostatic volume, and less PVR volume) by patients of group-B compared to those of group-A, this difference did not reach the statistical significance level (Table 2). No adverse events related to cholecalciferol use were reported among patients of group-B. Tamsulosin-related adverse effects among the study population were dizziness (two patients in group-A and three in group-B), weakness (two patients in group-A and three in group-B), and nausea (a single patient in group-A).

All patients with recurrent UTI had pyuria on urinalysis and positive culture of urine (Table 3). Regarding the clinical pattern of recurrent UTI, the most frequent one was cystitis (54.3%) with an undetermined pattern among 45.7% of patients. All cases of prostatitis and/or pyelonephritis had concomitant cystitis. Hematuria was more frequent among patients of group-A compared to those of group-B (6% vs. 1%). All patients of group-B were afebrile, and none of them had pyelonephritis. There was no significant difference regarding the clinical pattern between patients of group-A compared to those of group-B. Supplementary Figure 1 shows the relative frequency of different clinical patterns of recurrent and solitary UTI among both groups of the study population with BPH. Regarding the microbiological pattern, the most frequent infectious agent was *Escherichia coli* (62.9%). *Pseudomonas* was isolated only from patients of group-A (two cases with prostatitis and a single case of pyelonephritis).

Discussion

The overall incidence rate of recurrent UTI among our study population was 9%, which is higher than the average community-based (5%) and patient-based (7.5%) prevalence rates among the elderly males aged 65–85 years [11]. The higher incidence rate of recurrent UTI among our study population compared to the globally reported rates could be attributed to the difference in risk factors of UTI, where all of our study patients had BPH. Enlargement of the prostate leads to bladder outflow obstruction and residual urine, with subsequent intra-prostatic reflux of infected urine and migration of bacteria into the prostatic ducts. In addition, the antibacterial activity of prostatic secretions decreases with older age. Both those mechanical and immunological factors can lead to chronic settlement of bacteria within the prostate and the seminal vesicles forming a nidus for infection [12]. As far as we know; this is the first study to explore the incidence of recurrent UTI among Egyptian patients with BPH.

The significantly higher incidence rate of recurrent UTI among group-A patients compared to those of group-B suggests that cholecalciferol supplementation has contributed to the prevention of recurrent UTI among BPH patients with moderate/severe symptoms. The protective role of vitamin D can be explained by immunological and the mechanical factors.

The immunological factor depends on the existence of vitamin D receptors in most of the immune system cells, including T lymphocytes, neutrophils, and

Table 3 Clinical and microbiological pattern of urinary infection among the BPH study population with recurrent UTI

	Group-A ($n = 26$)	Group-B ($n = 9$)	Total ($n = 35$)	p value
Fever	6 (23.1)	0	6 (17.1)	na
Dysuria	13 (50)	3 (33.3)	16 (45.7)	0.094
Pyuria	26 (100)	9 (100)	35 (100)	0.382
Hematuria	12 (46.2)	2 (22.2)	14 (40)	0.058
Clinical pattern				
Cystitis	15 (57.7)	4 (44.4)	19 (54.3)	0.175
Prostatitis	11 (42.3)	2 (22.2)	13 (37.1)	0.063
Pyelonephritis	3 (11.5)	0	3 (8.6)	na
Undetermined	11 (42.3)	5 (55.6)	16 (45.7)	0.206
Positive urine culture	26 (100)	9 (100)	35 (100)	0.419
Escherichia coli	15 (57.7)	7 (77.8)	22 (62.9)	0.181
Enterococci	5 (19.3)	1 (11.1)	6 (17.1)	0.071
Proteus	3 (11.5)	1 (11.1)	4 (11.4)	0.334
Pseudomonas	3 (11.5)	0	3 (8.6)	na

na not applicable

antigen-presenting cells such as macrophages and dendritic cells [13, 14]. Vitamin D can induce production and secretion of the bladder epithelial cell-related antimicrobial peptide cathelicidin [15, 16]. In addition, vitamin D can increase the motility of neutrophils, enhancing the defense of innate immunity against bacterial infections [17] and promotes the antimicrobial properties of macrophages and monocytes through toll-like receptor signaling, monocyte-induced cytochrome (CYP27B1), inflammatory response in macrophages with enhanced secretion of cytokines, and enhanced capacity of monocyte-derived macrophages [18, 19]. Supporting the role of the immunological factor, Jorde et al. reported that supplementation of vitamin D (20,000 IU/week for 5 years) has resulted in prevention of UTI among males, but not females, patients with prediabetes; this observation was in agreement with the results of our study [20].

Regarding the mechanical factor, it has two components: prostatic and vesical. Supplemental vitamin D is inversely associated with the prevalence of BPH [21]. Vitamin D regulates the growth of prostatic cell that could influence the development of BPH and contributes to the arrest of prostate growth and consequently decrease the likelihood of UTI [22–24]. In addition, vitamin D is an effective antiproliferative agent of prostatic epithelium and stromal fibroblasts [25] through inhibition of the cell cycle and promotion of cellular apoptosis [26, 27] and inhibition of interleukin-8 with subsequent inhibition of cell proliferation (either directly or indirectly through reduced cyclooxygenase-2 expression and prostaglandin-2 production) [28]. The extra-prostatic effect of vitamin D exists through improving the pelvic floor contractility and the urinary bladder emptying by direct effect on muscle function [29]. The results of Murphy et al. showing inverse association between vitamin D levels with the overall prostate volume in patients with BPH support the mechanical factor [30].

The observation of significantly lower values of the difference of PVR volume between before and after treatment, and the levels of PSA among group-B patients compared to those of group-A of our study population with BPH was in agreement with the mechanical factor. However, the lower relative frequency of prostatitis among patients with recurrent UTI of group-B compared to those of group-A (22.2% vs. 42.3%) can represent a confounding factor.

We believe that adjuvant cholecalciferol supplementation needs to be encouraged for BPH patients with moderate/severe symptoms receiving tamsulosin therapy. Although not previously recommended, the use of cholecalciferol supplementation can protect such patients from recurrent UTI according to the results of our study.

The limitation of this study was the lack of laboratory confirmation of vitamin D deficiency by estimating the serum levels of vitamin D; the diagnosis relied on the clinical evaluation, solely. However, the dose of vitamin D supplementation used was equal for all patients regardless of their vitamin D status before treatment using the maximum recommended daily allowance by the WHO ensuring the adequacy of the supplementation without any potential toxicity. Considered as another limitation, this is study was not controlled using a placebo. Silodosin, which is the best currently available alpha-blocker for treatment of BPH, was not used; instead, we used tamsulosin, which was more widely available than silodosin during the study period. However, this study has a point in favor; it is the first one to explore the role of vitamin D in prevention of recurrent UTI among a vulnerable population of elderly patients with BPH as far as we know.

Conclusions

In conclusion, adjuvant cholecalciferol supplementation may be protective against recurrent UTI among patients with BPH receiving tamsulosin therapy without extra adverse effects. Before recommending the routine use of cholecalciferol supplementation for prevention of recurrent UTI, larger scale studies are recommended. The potential for the contribution of cholecalciferol supplementation to the therapeutic response of tamsulosin needs further studies to be thoroughly explored. Being inexpensive and safe, the use of vitamin D supplementation within the recommended dietary allowance range can be encouraged among patients with BPH receiving tamsulosin or other alpha-blockers.

Author contributions ASS: project development, data collection, data analysis, and manuscript writing. AH: project development, data collection, data analysis, and manuscript writing. AS: data collection and manuscript writing. MA: manuscript revision and manuscript editing. HO: manuscript revision and manuscript editing. SKA: data collection and manuscript writing. AN: data collection and manuscript editing. SB: data collection and manuscript editing. MS: manuscript revision and manuscript editing.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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