

# AMCoR

Asahikawa Medical University Repository <http://amcor.asahikawa-med.ac.jp/>

Lower urinary tract symptoms (2015.1) 7(1):37-41.

Improvement of Overactive Bladder Symptoms and Bladder Ischemia with Dutasteride in Patients with Benign Prostatic Enlargement.

Wada Naoki, Matsumoto Seiji, Kita Masafumi, Hashizume Kazumi, Kakizaki Hidehiro.

**Title page****Improvement of Overactive Bladder Symptoms and Bladder Ischemia  
with Dutasteride in Patients with Benign Prostatic Enlargement**

Naoki Wada, Seiji Matsumoto, Masafumi Kita, Kazumi Hashizume, Hidehiro Kakizaki

Department of Renal and Urologic Surgery, Asahikawa Medical University

Corresponding to: Naoki Wada, M.D, Ph.D

Department of Renal and Urologic Surgery, Asahikawa Medical University

2-1-1-1 Midorigaoka Higashi, Asahikawa, 078-8510, Japan

E-mail : [nwada@asahikawa-med.ac.jp](mailto:nwada@asahikawa-med.ac.jp)

TEL : +81 166 68 2533

FAX : +81 166 68 2539

**Running title:** dutasteride and bladder ischemia

## ABSTRACT AND KEY WORDS

### Objectives

**To evaluate the correlation of clinical and urodynamic parameters with bladder vascular resistance before and after dutasteride treatment in patients with lower urinary tract symptoms associated with benign prostatic enlargement.**

### Methods

A prospective study was conducted in consecutive 30 patients with benign prostatic enlargement who had not been satisfied with alpha-adrenergic antagonist monotherapy. Before and 24 weeks after dutasteride add-on treatment, we assessed IPSS, prostate volume (PV), urodynamic study and contrast-enhanced color Doppler ultrasonography to measure bladder vascular resistive index (RI).

### Results

Twenty-four weeks after dutasteride, PV significantly decreased from  $68\pm 29$  to  $48\pm 28$  ml ( $p<0.001$ ), and there was significant improvement of IPSS (from  $18.8\pm 7.7$  to  $13.4\pm 7.2$ ,  $p<0.001$ ). Urgency score of IPSS was also significantly improved from  $2.3\pm 1.9$  to  $1.4\pm 1.4$  ( $p<0.01$ ) after dutasteride. On pressure-flow study, bladder outlet obstruction index (BOOI) (from  $58\pm 36$  to  $38\pm 27$ ,  $p<0.001$ ) and detrusor pressure at Qmax (PdetQmax) (from  $73\pm 34$  to  $54\pm 25$  cmH<sub>2</sub>O,  $p<0.001$ ) were significantly improved. RI significantly decreased after dutasteride (from  $0.548\pm 0.069$  to  $0.486\pm 0.064$ ,  $p<0.001$ ). In 20 patients with persistent urgency after dutasteride, RI was less improved than in other 10 patients without urgency (change of RI  $0.045\pm 0.091$  vs.  $0.096\pm 0.042$ ,  $p<0.05$ ). Posttreatment BOOI and PdetQmax in patients with persistent urgency was significantly higher than in those without urgency after dutasteride (BOOI:  $46\pm 28$  vs.  $24\pm 20$ ,  $p<0.05$ , PdetQmax:  $62\pm 26$  vs.  $40\pm 17$  cmH<sub>2</sub>O,  $p<0.01$ ).

**Conclusions**

Reduction of obstruction and improvement of bladder ischemia **might** play an important role in a beneficial impact of dutasteride on overactive bladder symptoms.

**Key words:** benign prostatic hyperplasia, bladder ischemia, dutasteride, lower urinary tract symptoms, overactive bladder

**TEXT****1. INTRODUCTION**

Benign prostatic obstruction (BPO) is diagnosed when the cause of bladder outlet obstruction (BOO) is known to be benign prostatic enlargement (BPE), due to histologic benign prostatic hyperplasia (BPH). In clinical practice, lower urinary tract symptoms (LUTS) suggestive of BPO (LUTS/BPO) in male patients are treated by pharmacological agents including  $\alpha$ -adrenergic antagonist and  $5\alpha$ -reductase inhibitor. Dutasteride, a dual  $5\alpha$ -reductase inhibitor, is used for treatment of LUTS associated with BPE. Previous studies showed that dutasteride with or without tamsulosin significantly improved not only voiding symptoms but also storage symptoms,<sup>1,2</sup> including urgency that is the key symptom of overactive bladder (OAB) defined by The International Continence Society (ICS).<sup>3</sup> However, there have been few reports that focused on the improvement of OAB by dutasteride and its mechanisms.

Experimental and clinical studies indicate that bladder ischemia is one of the important pathophysiological factors of OAB. We previously examined bladder vascular resistance by using color Doppler ultrasonography (CDUS) in patients with LUTS/BPO before and after TURP.<sup>4</sup> In that study, we showed that higher bladder vascular resistance (bladder ischemia) before TURP was associated with higher degree of BOO and TURP decreased bladder vascular resistance. We also showed that less improvement of bladder vascular resistance after TURP was associated with postoperative persistent OAB, implying that improvement of bladder ischemia is one of the critical factors for the improvement of OAB symptoms. Because dutasteride can reduce prostate size and relieve obstruction in patients with BPE,<sup>5</sup> we hypothesized that dutasteride improves bladder ischemia and OAB symptoms in patients with BPE. In this prospective study, we evaluated the correlation of clinical and urodynamic

parameters with bladder vascular resistance before and after dutasteride treatment in patients with LUTS associated with BPE.

## 2. METHODS

This study was approved by Asahikawa Medical University Ethical Committee and carried out in accordance with the principles of the Declaration of Helsinki. Each patient was informed of the nature and purpose of the study and informed consent was obtained.

A prospective study was conducted in consecutive 30 patients with LUTS associated with BPE who had not been satisfied with  $\alpha$ -adrenergic antagonist monotherapy. Inclusion criteria were prostatic volume (PV)  $\geq 30$  ml and IPSS  $\geq 8$  or QOL index  $\geq 3$  under administration of any alpha-adrenergic antagonist (silodosin in 21 patients, tamsulosin in 6, and naftopidil in 3) without anticholinergic agent. Before and 24 weeks after dutasteride (0.5 mg daily) add-on treatment with preceding alpha-adrenergic antagonist, we assessed IPSS, PV, uroflowmetry (UFM), filling cystometry, pressure-flow study (PFS) and CDUS. The dose of alpha-adrenergic antagonist was not changed during the 24-week study period.

Urodynamic assessment included filling cystometry and PFS. Filling cystometry was performed with normal saline solution at a filling rate of 50 ml/min. A 6Fr double-lumen transurethral catheter was used for infusion and recording intravesical pressure, and a hand-made intrarectal balloon catheter was used for recording abdominal pressure. The severity of obstruction was assessed using the bladder outlet obstruction index (BOOI) formerly known as the Abrams-Griffiths number, defined as detrusor pressure at maximum flow rate (PdetQmax) - 2Qmax.<sup>6</sup> Detrusor overactivity (DO) was defined as involuntary detrusor contraction during filling phase irrespective of its amplitude. Otherwise the methods, definition,

and units for filling cystometry conformed to the standards proposed by the ICS.<sup>3</sup>

Bladder vascular resistive index (RI) was measured by enhanced CDUS with ultrasound contrast agent (Levovist®, Bayer, Tokyo, Japan), as previously reported (**Figure 1**).<sup>4</sup> CDUS was performed by one examiner (NW) with ProSound SSD-5500 (ALOKA, Tokyo, Japan) equipped with a 5.0-MHz probe. CDUS was performed during the storage phase without urge to void with bladder volume between 100 and 150 ml. After the administration of contrast agent, arterial blood flow of lateral bladder wall was examined by a transabdominal ultrasonography. RI ( $V_{max}-V_{min} / V_{max}$ ) was measured and the average RI of right and left vessels was calculated.

**To evaluate the correlation of clinical and urodynamic parameters with bladder vascular resistance before and after dutasteride treatment, we used Spearman's correlation for correlation analysis.** To identify differences between before and 24 weeks after dutasteride treatment and between the patients with and without persistent urgency after dutasteride, a paired t-test and Student's t test was used, respectively. **Persistent urgency was defined as  $\geq 1$  point of question 4 of the IPSS after dutasteride treatment.**  $P < 0.05$  was considered statistically significant.

### 3. RESULTS

The characteristics of the 30 patients who were treated with dutasteride add-on are shown in Table 1. The mean age and PV of the study patients were 73.6 years (range 60-83) and 68 ml (30-139), respectively. On filling cystometry, DO was shown in 23 patients (77%).

Pretreatment RI did not statistically correlate with age ( $r=-0.14$ ), IPSS ( $r=0.08$ ), maximum flow rate ( $Q_{max}$ ) ( $r=0.18$ ), PV ( $r=0.22$ ,  $P>0.05$ ), BOOI ( $r=-0.04$ ) or  $P_{det}Q_{max}$  ( $r=-0.02$ ).

**There was no difference in pretreatment RI among three alpha-adrenergic antagonists.**

When the study patients were dichotomized using several cut-off values of these parameters, RI was significantly higher in patients with  $PV \geq 60$  ml ( $n=18$ ) than in those with  $PV < 60$  ml ( $n=12$ ) ( $0.570 \pm 0.049$  versus  $0.514 \pm 0.083$ ,  $p < 0.05$ ). There was no significant difference in pretreatment RI among patients with different numbers of vascular risk factors or between patients with and without DO.

Twenty-four weeks after treatment with dutasteride, IPSS (from  $18.8 \pm 7.7$  to  $13.4 \pm 7.2$ ,  $p < 0.001$ ) and QoL index (from  $4.6 \pm 1.0$  to  $3.4 \pm 1.3$ ,  $p < 0.001$ ) were significantly improved (Table 2). Sub-scores of IPSS except Q6 (straining) were also significantly improved by dutasteride.

**Serum PSA level significantly decreased and serum testosterone level significantly**

**increased after dutasteride.** Qmax (from  $12.2 \pm 6.1$  ml/sec to  $13.3 \pm 7.7$  ml/sec,  $p = 0.09$ ) and postvoid residual (from  $93 \pm 88$  ml to  $127 \pm 121$  ml,  $p = 0.17$ ) did not change significantly. On PFS, BOOI (from  $58 \pm 36$  to  $38 \pm 27$ ,  $p < 0.001$ ) and PdetQmax (from  $73 \pm 34$  cmH<sub>2</sub>O to  $54 \pm 25$  cmH<sub>2</sub>O,  $p < 0.001$ ) were significantly improved. Overall RI significantly decreased after treatment with dutasteride (from  $0.548 \pm 0.069$  to  $0.486 \pm 0.064$ ,  $p < 0.001$ ) (Table 2). **There was**

**no difference in posttreatment RI among three alpha-adrenergic antagonists.**

**Posttreatment RI did not correlate with age, posttreatment PV, IPSS, BOOI or**

**PdetQmax.**

We additionally explored the correlation between persistent urgency and reduction of RI after dutasteride treatment. In 20 patients (67%) with persistent urgency after dutasteride, the reduction of RI was significantly less than in other 10 patients (33%) without urgency after dutasteride ( $0.045 \pm 0.091$  versus  $0.096 \pm 0.042$ ,  $p = 0.04$ ) (Table 3). Posttreatment PdetQmax and BOOI in patients with persistent urgency were significantly higher than in those without



urgency after dutasteride (PdetQmax:  $62 \pm 26$  cmH<sub>2</sub>O versus  $40 \pm 17$  cmH<sub>2</sub>O,  $p = 0.009$ , BOOI:  $46 \pm 28$  versus  $24 \pm 20$ ,  $p = 0.019$ ), although these two parameters before dutasteride were not significantly different between the patients with and without persistent urgency (Table 3). Age and PV before and after dutasteride were not significantly different between the patients with and without persistent urgency. Total IPSS before and after dutasteride was significantly higher in patients with persistent urgency than in those without urgency after dutasteride. In patients with persistent urgency, prevalence of DO after dutasteride was 70% (14 of 20 patients) compared to 40% (4 of 10 patients) in those without urgency after dutasteride ( $p=0.11$ ). Prevalence of hypertension, hyperlipidemia and diabetes was not significantly different between the patients with and without persistent urgency.

#### 4. DISCUSSION

The present study that was conducted with the same approach as our previous report <sup>4</sup> suggests that bladder vascular resistance in patients with BPE is elevated in correlation with PV, and that whether urgency resolves or persists after dutasteride treatment is related to the degree of reduction of bladder vascular resistance along with the improvement of obstruction. These findings imply that reduction of obstruction and amelioration of bladder ischemia by dutasteride is an important factor for improvement of OAB symptoms in patients with LUTS associated with BPE.

In accordance with previous reports <sup>1,2</sup>, the present study confirmed that 24-week treatment of dutasteride reduced prostate size and improved voiding and storage symptoms including urinary urgency. We previously examined urodynamic effects of dutasteride on BOO and bladder storage function and showed that dutasteride relieved obstruction and improved bladder

storage function.<sup>5</sup> The present study confirmed the beneficial effect of dutasteride in relieving obstruction and improving bladder storage function. The present study further examined RI as a reflection of bladder vascular resistance before and after dutasteride treatment.

Overall RI significantly decreased after dutasteride treatment (from  $0.548 \pm 0.069$  to  $0.486 \pm 0.064$ ,  $p < 0.001$ ), implying that dutasteride significantly increased bladder blood flow. It is well known that BOO induces bladder ischemia in men with LUTS/BPO.<sup>4, 7, 8</sup> Plenty of animal experiments demonstrate the relationship between BOO and bladder ischemia.<sup>9-11</sup> High voiding pressure, bladder overdistension and thick bladder wall associated with BOO seem to result in compression of intramural vessels and produce bladder ischemia. On the other hand, a previous study showed that thick bladder wall and bladder hypertrophy were reversibly improved after surgical relief of obstruction in men with BPE.<sup>12</sup> Thus, relief of obstruction can lead to improvement of bladder blood flow through the reduction of intramural tension and bladder vascular resistance. Interestingly, the patients with no posttreatment urgency had lower BOOI and PdetQmax and better improvement of RI after dutasteride than those with persistent urgency. It seems that reduction of obstruction and improvement of bladder ischemia by dutasteride is a critical factor for resolution of OAB symptoms in patients with LUTS associated with BPE. If we compare pretreatment parameters between patients with or without persistent urgency after dutasteride (Table 3), those with persistent urgency had larger PV, higher IPSS, BOOI and PdetQmax than those without persistent urgency with a statistical significance noted only in IPSS. Because the number of patients was very small in the present study, further study with a large number of patients could identify pretreatment predictive factors for resolution of OAB symptoms with dutasteride treatment.

Our previous study showed that male OAB patients with low serum testosterone level at

baseline had better improvement of OAB symptoms after dutasteride add-on therapy than those with normal testosterone level at baseline.<sup>13</sup> The change of serum testosterone is considered as another factor accounting for improvement of bladder blood flow by dutasteride. Dutasteride is known to reduce serum and intraprostatic dihydrotestosterone concentrations by inhibition of 5 $\alpha$ -reductase type 1 and 2.<sup>14, 15</sup> As a result, dutasteride causes a slight increase in serum testosterone level. The increase in serum testosterone after dutasteride treatment is higher in patients with low serum testosterone at baseline.<sup>16</sup> Furthermore, a favorable level of serum testosterone was reported to have a protective effect on arterial aging, stiffness and elasticity.<sup>17</sup> Therefore, increase in testosterone level by dutasteride might be a contributing factor to the improvement of bladder ischemia.

Despite a small number of the study patients, we believe that improvement of bladder blood flow by dutasteride is an important factor for resolution of OAB symptoms. During this study, Levovist®, ultrasound contrast agent, has been discontinued and we could not increase further study patients. Further research with ultrasonography targeting bladder ischemia will lead to medical care with better quality for male patients with OAB associated with LUTS/BPO.

In conclusion, relief of obstruction and improvement of bladder ischemia **might** contribute to a beneficial impact of dutasteride on bladder storage function and storage symptoms.

## **Disclosure**

There is no involvement, financial or otherwise.

## REFERENCES

- 1 Becher E, Roehrborn CG, Siami P et al: The effects of dutasteride, tamsulosin, and the combination on storage and voiding in men with benign prostatic hyperplasia and prostatic enlargement: 2-year results from Combination of Avodart and Tamsulosin Study. *Prostate Cancer Prostatic Dis* 2009; 12: 369-74.
- 2 Tsukamoto T, Shirai T, Sakamoto S et al: The effect of dutasteride on voiding and storage symptoms in men with benign prostatic hyperplasia. *Acta Urol Jpn* 2010; 56: 677-82.
- 3 Abrams P, Cardozo L, Fall M et al The standardization of the terminology of lower urinary tract function: Report from the standardisation sub-committee of the International Continence Society. *Neurourol Urodyn* 2002; 21: 167-78.
- 4 Wada N, Watanabe M, Kita M et al. Analysis of bladder vascular resistance before and after prostatic surgery in patients with lower urinary tract symptoms suggestive of benign prostatic obstruction. *Neurourol Urodyn* 2012; 31: 659-63.
- 5 Wada N, Kita M, Hashizume K et al. Urodynamic effects of dutasteride add-on therapy to alpha-adrenergic antagonist for patients with benign prostatic enlargement: prospective pressure-flow study. *Neurourol Urodyn* 2013; 32: 1123-7.
- 6 Abrams P. Bladder outlet obstruction index, bladder contractility index and bladder voiding efficacy: three simple indices to define bladder voiding function. *BJU Int* 1999; 84: 14-5
- 7 Lin AT, Chen MT, Yang CH et al. Blood flow of the urinary bladder: effects of outlet obstruction and correlation with bioenergetic metabolism. *Neurourol Urodyn* 1995; 14: 285-92.
- 8 Mitterberger M, Pallwein L, Gradl J et al. Persistent detrusor overactivity after transurethral resection of the prostate is associated with reduced perfusion of the urinary bladder. *BJU Int*

2007; 99: 831-35.

9 Matsumoto S, Chichester P, Kogan BA et al. The structural and vascular response of normal and obstructed rabbit whole bladders to distention. *Urology* 2003; 62: 1129-33.

10 Chichester P, Schroder A, Horan P et al. Vascular response of the rabbit bladder to chronic partial outlet obstruction. *Mol Cell Biochem* 2001; 226: 1-8.

11 Schroder A, Chichester P, Kogan BA et al. Effect of chronic bladder outlet obstruction on blood flow of the rabbit bladder. *J Urol* 2001; 165: 640-46.

12 Kojima M, Inui E, Ochiai A et al. Reversible change of bladder hypertrophy due to benign prostatic hyperplasia after surgical relief of obstruction. *J Urol* 1997; 158: 89-93.

13 Wada N, Hashidume K, Tamaki G et al. Add-on effect of dutasteride in patients with benign prostatic hyperplasia treated with alpha blocker : its effect on overactive bladder. *Acta Urol Jap* 2012; 58: 475-80.

14 Clark RV, Hermann DJ, Cunningham GR, et al. Marked suppression of dihydrotestosterone in men with benign prostatic hyperplasia by dutasteride, a dual 5 $\alpha$ -reductase inhibitor. *J Clin Endocrinol Metab* 2004; 89: 2179-84.

15 Wurzel R, Ray P, Major-Walker K, et al. The effect of dutasteride on intraprostatic dihydrotestosterone concentrations in men with benign prostatic hyperplasia. *Prostate Cancer Prostatic Dis* 2007; 10: 149-54.

16 Hong SK, Min GE, Ha SB et al. Effect of the dual 5 $\alpha$ -reductase inhibitor, dutasteride, on serum testosterone and body mass index in men with benign prostatic hyperplasia. *BJU Int* 2010; 105: 970-4.

17 Dockery F, Bulpitt CJ, Donaldson M et al. The relationship between androgens and arterial stiffness in older men. *J Am Geriatr Soc* 2003; 51: 1627-32.

**Figure legend**

**Figure 1. Transabdominal enhanced color Doppler ultrasonography**

Table1 Characteristics of study patients

Age, yrs (range)	73.6 (60- 83)
Prostate volume, ml (range)	68 (30- 139)
<b>【Vascular risk factor】</b>	
Hypertension, <i>n</i> (%)	14 (47%)
Hyperlipidemia , <i>n</i> (%)	6 (20%)
Diabetes , <i>n</i> (%)	5 (17%)
IPSS, (range)	18.8 (4- 32)
QoL index, (range)	4.6 (2- 6)
<b>【Urodynamics parameters】</b>	
Maximum flow rate, ml/s (range)	12.2 (4.6- 32.0)
Postvoid residual, ml (range)	93 (0- 455)
BOOI, (range)	58 (7 - 134)
PdetQmax, cmH2O (range)	73 (21- 147)
Detrusor overactivity Present , <i>n</i> (%)	23 (77%)
BOOI: bladder outlet obstruction index	

Table2 Change of parameters before and after dutasteride treatment

	Before dutasteride	24 weeks after dutasteride	P value
IPSS	18.8 ± 7.7	13.4 ± 7.2	<0.001
Q1 (feeling of incomplete emptying)	2.5 ± 1.9	1.7 ± 1.7	0.01
Q2 (increased daytime frequency)	3.3 ± 1.7	2.3 ± 1.7	<0.001
Q3 (intermittent stream)	2.3 ± 2.0	1.7 ± 1.6	<0.05
Q4 (urinary urgency)	2.3 ± 1.9	1.4 ± 1.4	<0.01
Q5 (slow stream)	3.3 ± 1.6	2.4 ± 1.5	<0.01
Q6 (straining)	2.1 ± 1.9	1.6 ± 1.5	0.10
Q7 (nocturia)	2.9 ± 1.3	2.3 ± 1.2	<0.001
QoL index	4.6 ± 1.0	3.4 ± 1.3	<0.001
PV (ml)	68 ± 29	48 ± 28	<0.001
Serum PSA (ng/ml)	6.9 ± 11.1	3.9 ± 6.6	<0.001
Serum testosterone (ng/dl)	380 ± 182	488 ± 193	<0.001
	<b>【Free uroflowmetry】</b>		
Voided volume (ml)	192 ± 107	227 ± 126	0.07
Qmax (ml/sec)	12.2 ± 6.1	13.3 ± 7.7	0.09
Postvoid residual (ml)	93 ± 88	127 ± 121	0.17
	<b>【Filling cystometry and PFS】</b>		
Prevalence of DO, <i>n</i> (%)	23 (77)	18 (60)	0.17*
PdetQmax (cmH2O)	73 ± 34	54 ± 25	<0.001
BOOI	58 ± 36	38 ± 27	<0.001
Bladder RI	0.548 ± 0.069	0.486 ± 0.064	<0.001
mean ± SD			
Using the Wilcoxon matched-pairs signet-ranks test except for prevalence of DO using Chi-square test*			



Table3 Differences of each parameter between patients with and without urgency after dutasteride

		Persistent urgency	No persistent urgency	<i>P value</i>
No. patients, <i>n</i> (%)		20 (67%)	10 (33%)	
Reduction of bladder RI		0.045±0.091	0.096±0.042	<0.05
Age ( <i>yrs</i> )		73.8±5.6	73.2±7.3	0.84
PV	before dutasteride ( <i>ml</i> )	71±28	61±30	0.37
	after dutasteride ( <i>ml</i> )	51±28	42±28	0.44
IPSS	before dutasteride	20.9±7.1	14.6±7.4	<0.05
	after dutasteride	15.8±7.0	8.8±5.6	<0.01
BOOI	before dutasteride	62±39	49±30	0.31
	after dutasteride	46±28	24±20	<0.05
PdetQmax	before dutasteride ( <i>cmH2O</i> )	78±35	62±30	0.20
	after dutasteride ( <i>cmH2O</i> )	62±26	40±17	<0.01
Prevalence of DO	before dutasteride, <i>n</i> (%)	16 (80)	7 (70)	0.52
	after dutasteride, <i>n</i> (%)	14 (70)	4 (40)	0.11
Vascular risk factors	Hypertention, <i>n</i> (%)	11 (55)	3 (30)	0.19
	Hyperlipidemia, <i>n</i> (%)	5 (25)	1 (10)	0.33
	Diabetes, <i>n</i> (%)	3 (15)	2 (20)	0.76

mean±SD

Using the Wilcoxon matched-pairs signet-ranks test except for prevalence of DO and vascular risk factors using Chi-square test

