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Relationship between lower urinary tract symptoms and urinary ATP in patients with benign prostatic hyperplasia or overactive bladder

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Abstract

We investigated whether the improvement of lower urinary tract symptoms (LUTS) and urinary adenosine triphosphate (ATP) level were related. Fifty-seven patients and 13 normal controls were enrolled in this study. All of the male patients had benign prostatic hyperplasia (BPH), and all of the female patients had overactive bladder (OAB). We administered an alpha-1 adrenergic receptor antagonist (tamsulosin hydrochloride) for BPH, while OAB patients received an anti-muscarinic agent (propiverine hydrochloride). Before and after treatment, we examined LUTS and urinary ATP/creatinine ratio. The urinary ATP/creatinine ratio was lower in males than females in both controls and patients. In the BPH patients, administration of the alpha-1 receptor antagonist decreased LUTS and urinary ATP/creatinine ratio, and improvement of LUTS was greater in patients with a high baseline urinary ATP level. In the OAB patients, administration of the anti-muscarinic agent decreased LUTS and urinary ATP/creatinine ratio, and improvement of LUTS was greater in patients with a high baseline urinary ATP level. Improvement of LUTS by treatment with the alpha-1 receptor antagonist or the anti-muscarinic agent was related to the decrease of urinary ATP/creatinine ratio in patients with BPH or OAB. Measurement of urinary ATP can be used as a marker of pathologic bladder function.

Alpha-1 adrenergic receptor antagonists are the first-line medications for the treatment of benign prostatic hyperplasia (BPH), because these drugs relax the smooth muscle in the prostate and decrease resistance to urine flow in the prostatic urethra (6, 10). These antagonists improve both urinary voiding disorders and urinary collecting disorders, while co-administration of the alpha-1 adrenergic receptor antagonist and the anti-muscarinic agent is more effective for controlling overactive bladder (OAB) in BPH patients (3). Anti-muscarinic agents are known to inhibit bladder smooth muscle contraction, and may possibly also block the effects of muscarinic receptors on bladder epithelial cells (12, 20).

Bladder epithelial cells exhibit a number of properties similar to those of neurons (nociceptors/mechanoreceptors), and both types of cells share several signal transduction mechanisms to detect physiological stimuli. Examples of neuronal sensory receptors that have been identified in the bladder epithelium include receptors for purine (15), noradrenaline (4), and acetylcholine (12, 13). Recent studies have also shown that intravenous administration of alpha-1 adrenergic receptor antagonists inhibits adenosine triphosphate (ATP) release into the bladder lumen as well as bladder afferent nervous activity (9), while application of muscarinic agonists provokes ATP release from cultured bladder epithelial cells (14). These results suggest that both alpha-1 adrenergic receptor antagonist and anti-muscarinic agents inhibit ATP secretion from the bladder epithelium, and

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this effect may be one of the reasons for improvement of urinary collecting disorders by these agents.

To confirm the influence of these agents on ATP secretion by the bladder epithelium, we previously examined the effects of chronic administration of the alpha-1 adrenergic receptor antagonist or the anti-muscarinic agent on urinary ATP levels before and after bladder stimulation with 0.1% acetic acid in rats. As the results, the urinary ATP level was significantly increased in control rats after bladder stimulation with acetic acid, but the increase of ATP level was smaller in alpha-1 adrenergic receptor antagonist-treated rats (62% of the control value) and anti-muscarinic agent-treated rats (45% of the control value)(16).

In the present study, we therefore examined whether the improvement of lower urinary tract symptoms (LUTS) and urinary ATP levels after medical treatment were also related in patients with BPH and/or OAB.

SUBJECTS AND METHODS

A total of 70 subjects were enrolled in this study, including 57 patients (27 men and 30 women aged 46–83 years) and 13 normal controls (7 men and 6 women aged 33–53 years) with no micturition disorders. The patients were selected from outpatients consulting the Department of Urology at our University Hospital or an affiliated hospital, and the normal controls were staff of our hospital. The mean (± standard deviation) age of the patients and normal controls was 69 ± 9 years (male: 68 ± 9, female: 69 ± 8) and 40 ± 8 years (male: 43 ± 9, female: 37 ± 6), respectively. All of the subjects gave informed consent to the study and the protocol was approved by the University of the Ryukyus and each affiliated hospital. All of the male patients had BPH and 10 of them also had OAB. The average prostate volume was 39 ± 19 (17–83) g and the prostate specific antigen (PSA) level was 1.0–9.7 ng/mL. All of the female patients had OAB, but the diseases causing OAB could not be identified. We administered an alpha-1 adrenergic receptor antagonist (tamsulosin hydrochloride at 0.2 mg once a day) for the treatment of BPH, and used an anti-muscarinic agent (propiverine hydrochloride at 20 mg once a day) for OAB. Patients who were taking both agents and/or herbal medicines were excluded from the study, as well as patients with urinary tract cancer, hematuria (urinary occult blood test $\geq$ 1+), proteinuria (urinary protein $\geq$ 1+), or pyuria (urinary leukocyte $\geq$ 10 cells/high power field: 400 × magnification level).

Before and after 4 weeks of treatment with the alpha-1 adrenergic receptor antagonist or anti-muscarinic agent, we determined the OAB Symptom Score (OABSS) (8), the International Prostatic Symptom Score (IPSS), and the Quality of Life (QOL) score. We also measured the urinary ATP level and urinary creatinine level. Each patient and control urinated into a clean cup when the desire for micturition was felt. The spot urine sample was collected and the urinary ATP level was immediately analyzed using an ATP Hygiene Kit HS (Bio Thema AB, Haninge, Sweden) and a Gene Light 55 (Microtec Nition, Funabashi, Japan). Then the ATP values were corrected by the urinary creatinine level (ATP/creatinine ratio). These parameters were compared between the two classes of agents, controls and patients, or before and after treatment.

Results are reported as the mean ± standard deviation (SD). Student's paired or unpaired *t*-test and regression analysis were used for statistical analysis, and $P < 0.05$ was considered to indicate statistical significance.

RESULTS

We examined the relations between sex, age and the urinary ATP/creatinine ratio. Among the normal controls, the urinary ATP/creatinine ratio was significantly lower ($P = 0.029$) in men (3.6 ± 1.7 mol/mg × E-10) than women (13.9 ± 12.9 mol/mg × E-10). Among the patients, the pretreatment urinary ATP/creatinine ratio was also significantly lower ($P = 0.007$) in male BPH patients (6.9 ± 3.3 mol/mg × E-10) than in female OAB patients (14.6 ± 15.4 mol/mg × E-10). Comparison of the controls and patients showed that the normal male controls (43 ± 9 years) and normal female controls (37 ± 6 years) were significantly younger ($P < 0.001$ each) than the male BPH patients (68 ± 9 years) and female OAB patients (69 ± 8 years), respectively. The urinary ATP/creatinine ratio was significantly lower ($P = 0.009$) in normal male controls than in BPH patients, but significant difference was not observed between normal female controls and OAB patients. There was no significant correlation between age and the urinary ATP/creatinine ratio in the male BPH patients (Fig. 1-A). However, the urinary ATP/creatinine ratio of the female OAB patients increased with age, and there was a positive correlation ($P = 0.034$) between age and this ratio ($y = 0.85x - 44$, $r = 0.449$) (Fig. 1-B).

In male BPH patients, the OABSS-total, IPSS-total, and QOL scores were all significantly de-

creased ($P < 0.01$ each) after 4 weeks of treatment with the alpha-1 adrenergic receptor antagonist compared with the values before administration (Table 1). The urinary ATP/creatinine ratio also showed a significant decrease ($P = 0.001$) after alpha-1 adrenergic receptor antagonist treatment, but there was no correlation between prostate size and this ratio.

We divided the BPH patients into 2 groups based on the median value of the urinary ATP/creatinine ratio before treatment (6.1 mol/mg × E-10). The patients with a urinary ATP/creatinine ratio > 6.1 mol/mg × E-10 formed the high ATP-BPH group (n = 15,

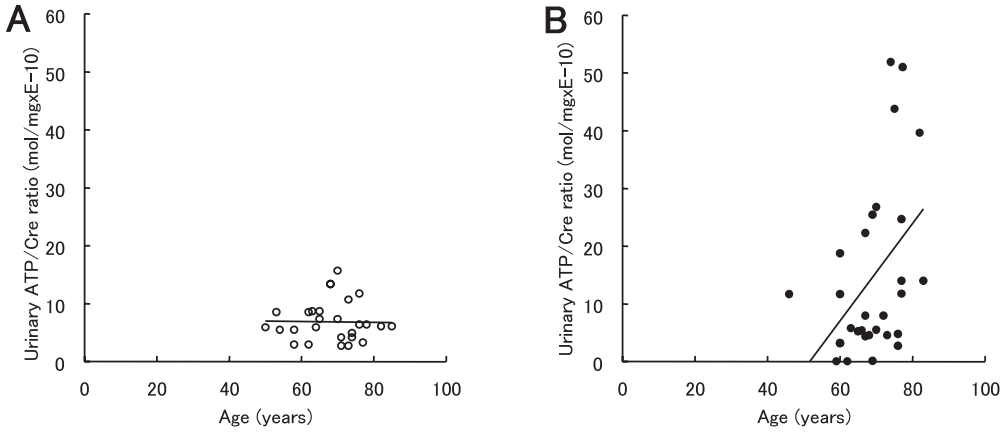

Fig. 1 Relations between sex, age, and the urinary ATP/creatinine ratio in male BPH patients (A) and female OAB patients (B). There was no significant correlation between age and the urinary ATP/creatinine ratio in male patients (A), but the urinary ATP/creatinine ratio of female patients increased with age and there was a correlation ($P = 0.034$) between age and the ratio ($y = 0.85x - 44$, $r = 0.449$) (B).

Table 1 *Change of urinary ATP/creatinine ratio and LUTS after administration of an alpha-1 adrenergic receptor antagonist in BPH patients*

	Before	After	*P*
The number of cases	27		
Age (years)	68 ± 9		
Urinary ATP/creatinine ratio (mol/mg × E-10)			
Average ± SD	6.9 ± 3.3	4.7 ± 3.0	0.001
Median level	6.1	4.2	
OABSS			
urinary frequency at daytime	0.5 ± 0.6	0.6 ± 0.7	0.188
urinary frequency at nighttime	2.3 ± 0.8	1.9 ± 0.7	< 0.001
urgency	1.6 ± 1.5	0.9 ± 1.4	0.005
incontinence	0.4 ± 0.8	0	0.006
OABSS-total	4.9 ± 2.3	3.4 ± 2.0	0.001
IPSS			
empty	1.2 ± 1.9	0.5 ± 1.3	0.028
frequency	1.8 ± 1.8	1.3 ± 1.6	0.028
intermittency	0.9 ± 1.8	0.7 ± 1.1	0.226
urgency	1.1 ± 1.2	0.7 ± 1.3	< 0.001
weak stream	2.6 ± 2.3	2.0 ± 2.2	0.111
hesitancy	0.5 ± 1.3	0.3 ± 0.6	0.141
nocturia	2.4 ± 0.9	1.9 ± 0.7	< 0.001
IPSS-total	10.5 ± 7.0	7.3 ± 4.7	< 0.001
QOL score	4.2 ± 1.0	3.2 ± 1.4	< 0.001

Mean ± SD

mean age of 70 ± 8 years), and those with a ratio ≤ 6.1 mol/mg × E-10 formed the low ATP-BPH group (n = 12, mean age of 66 ± 9 years). We examined the relation between LUTS and the urinary ATP/creatinine ratio in both groups. There was no significant difference of mean age between the high ATP-BPH group and the low ATP-BPH group. In the high ATP-BPH group, some parameters of urinary voiding disorders (IPSS-intermittency, weak stream, and hesitancy), as well as IPSS-total and the QOL score, were significantly higher (all $P < 0.05$) compared with the findings in the low ATP-BPH group. These parameters (except hesitancy) and some parameters of urinary collecting disorders (IPSS-urgency and nocturia) showed a significant decrease (all $P < 0.05$) after treatment with the alpha-1 adrenergic receptor antagonist, along with a significant decrease ($P = 0.004$) of the urinary ATP/creatinine ratio (Table 2). In the low ATP-BPH group, some parameters of urinary collecting disorders (OABSS-incontinence and OABSS-total) were significantly higher (both $P = 0.003$) compared with the findings in the high ATP-BPH group. These parameters and other parameters of urinary collecting disorders (IPSS-frequency, urgency, and nocturia), as well as the QOL score, showed a significant decrease (all $P < 0.05$) after treatment with the alpha-1 adrenergic receptor antagonist, although the urinary ATP/creatinine ratio did not change (Table 2).

We also examined the relations between LUTS and the urinary ATP/creatinine ratio in BPH patients with OAB (BPH-OAB group, n = 10) or without OAB (BPH-non OAB group, n = 17). The BPH-OAB group was significantly younger (64 ± 8 years) and their urinary ATP/creatinine ratio before treatment (4.8 ± 2.2 mol/mg × E-10) was significantly lower (both $P < 0.05$) compared with the BPH-non OAB group (71 ± 8 years and 8.1 ± 3.3 mol/mg × E-10). However, the OABSS-total, IPSS-frequency score, and IPSS-urgency score were all significantly ($P < 0.05$) higher in the BPH-OAB group (7.4 ± 1.1, 2.6 ± 2.0 and 2.0 ± 1.6) compared with the BPH-non OAB group (3.4 ± 1.2, 1.3 ± 1.6 and 0.6 ± 0.5), respectively.

In female OAB patients, the OABSS-total, IPSS-total, and QOL scores were all significantly decrease

Table 2 *Change of urinary ATP/creatinine ratio and LUTS after administration of an alpha-1 adrenergic receptor antagonist in high ATP-BPH group and low ATP-BPH group*

	High ATP-BPH group			Low ATP-BPH group		
	Before	After	*P*	Before	After	*P*
The number of cases	15			12		
Age (years)	70 ± 8			66 ± 9		
Urinary ATP/creatinine ratio (mol/mg × E-10)	9.1 ± 2.7 ***	6.1 ± 3.3	0.004	4.1 ± 1.3	3.1 ± 1.7	0.083
OABSS						
urinary frequency at daytime	0.4 ± 0.5	0.7 ± 0.7	0.010	0.7 ± 0.8	0.5 ± 0.8	0.219
urinary frequency at nighttime	2.3 ± 0.8	1.9 ± 0.6	0.007	2.3 ± 0.8	1.8 ± 0.7	0.026
urgency	1.3 ± 1.6	0.9 ± 1.8	0.028	2.0 ± 1.3	0.8 ± 0.9	0.021
incontinence	0	0	–	1.0 ± 1.0*	0	0.003
OABSS-total	4.0 ± 1.9	3.5 ± 2.2	0.075	6.0 ± 2.3*	3.2 ± 1.9	0.003
IPSS						
empty	1.5 ± 2.2	0.8 ± 1.7	0.091	0.8 ± 1.5	0.2 ± 0.4	0.097
frequency	1.5 ± 1.6	1.5 ± 1.7	0.335	2.2 ± 2.0	1.0 ± 1.5	0.011
intermittency	1.7 ± 2.1**	0.7 ± 0.7	0.015	0	0.7 ± 1.6	0.083
urgency	1.3 ± 1.6	0.9 ± 1.7	0.004	1.0 ± 0.6	0.5 ± 0.5	0.026
weak stream	3.8 ± 2.1***	2.7 ± 2.4	0.024	1.0 ± 1.5	1.2 ± 1.9	0.411
hesitancy	0.9 ± 1.6*	0.4 ± 0.7	0.067	0	0.2 ± 0.4	0.083
nocturia	2.5 ± 1.0	1.9 ± 0.6	0.001	2.3 ± 0.8	1.8 ± 0.7	0.026
IPSS-total	13.1 ± 8.2*	8.8 ± 5.5	< 0.001	7.3 ± 3.2	5.5 ± 2.6	0.137
QOL score	4.5 ± 0.9*	3.5 ± 1.5	0.011	3.8 ± 0.9	2.8 ± 1.3	0.019

Mean ± SD

High ATP-BPH group: patients with a urinary ATP/creatinine ratio over 6.1 mol/mg × E-10 before treatment.

Low ATP-BPH group: patients with a urinary ATP/creatinine ratio under 6.1 mol/mg × E-10 before treatment.

*: $P < 0.05$, **: $P < 0.01$, ***: $P < 0.001$, compared the baseline levels (before) between high ATP-BPH group and low ATP-BPH group.

($P < 0.001$ each) after 4 weeks of treatment with the anti-muscarinic agent, along with a significant decrease ($P = 0.013$) of the urinary ATP/creatinine ratio (Table 3).

We divided the female OAB patients into 2 groups based on the median value of the urinary ATP/creatinine ratio before treatment (8.0 mol/mg × E-10). The patients with a urinary ATP/creatinine ratio > 8.0 mol/mg×E-10 formed the high ATP-OAB group (n = 14, mean age of 71 ± 12 years), and those with a ratio ≤ 8.0 mol/mg × E-10 formed the low ATP-OAB group (n = 16, mean age of 67 ± 6 years). The relation between LUTS and the urinary ATP/creatinine ratio was examined in both groups. There was no significant difference of mean age between the high ATP-OAB group and low ATP-OAB group (Table 4). In the high ATP-OAB group, the IPSS-frequency score and QOL score were significantly higher ($P < 0.01$ each) compared with the findings in the low ATP-OAB group. These parameters and other IPSS parameters (intermittency, urgency, nocturia, and IPSS-total), as well as OABSS-total, showed a significant decrease (all $P < 0.05$) after treatment with the anti-muscarinic agent, along with a significant decrease ($P = 0.003$) of the urinary ATP/creatinine ratio. In the low ATP-OAB group, some parameters of urinary collecting disorders (OABSS-total, IPSS-urgency, nocturia, and IPSS-total) and the QOL score showed a significant decrease ($P < 0.05$ each) after treatment with the anti-muscarinic agent, although the IPSS-frequency score and the urinary ATP/creatinine ratio did not change (Table 2).

DISCUSSION

In our previous study using a female rat model (16), chronic administration of the alpha-1 adrenergic receptor antagonist (naftopidil) and the anti-muscarinic agent (propiverine hydrochloride) did not influence cystometric parameters or the urinary ATP/creatinine ratio before bladder stimulation. After stimulation of the bladder by infusion of acetic acid, urinary frequency, high pressure bladder contractions, and an increase of the urinary ATP/creatinine ratio were induced in untreated rats. However, pretreatment with the alpha-1 adrenergic receptor antagonist prevented urinary frequency and an increase of the urinary ATP/creatinine ratio, and pretreatment with the anti-muscarinic agent inhibited urinary fre-

Table 3 *Change of urinary ATP/creatinine ratio and LUTS after administration of an anti-muscarinic agent in female OAB patients*

	Before	After	*P*
The number of cases	30		
Age (years)	60 ± 8		
Urinary ATP/creatinine ratio (mol/mg × E-10)			
Average ± SD	14.6 ± 15.4	10.2 ± 10.3	0.013
Median level	8.0	5.2	
OABSS			
urinary frequency at daytime	0.8 ± 0.6	0.5 ± 0.6	0.002
urinary frequency at nighttime	2.0 ± 0.9	1.4 ± 1.1	< 0.001
urgency	3.3 ± 1.7	1.9 ± 2.0	< 0.001
incontinence	2.7 ± 2.1	1.4 ± 1.9	< 0.001
OABSS-total	8.8 ± 3.7	5.1 ± 4.3	< 0.001
IPSS			
empty	0.7 ± 1.5	0.5 ± 1.3	0.103
frequency	2.6 ± 1.7	1.3 ± 1.6	< 0.001
intermittency	0.3 ± 0.4	0.1 ± 0.3	0.029
urgency	2.4 ± 1.7	0.8 ± 1.1	< 0.001
weak stream	1.0 ± 1.7	0.7 ± 1.5	0.087
hesitancy	0.2 ± 0.8	0.2 ± 0.9	0.163
nocturia	2.1 ± 1.1	1.4 ± 1.2	< 0.001
IPSS-total	9.3 ± 5.2	5.1 ± 5.5	< 0.001
QOL score	5.3 ± 0.8	3.3 ± 1.7	< 0.001

Mean ± SD

quency, high pressure bladder contractions, and an increase of the urinary ATP/creatinine (16). In the present study, the clinical findings were similar to the results obtained in our animal model, and the current data confirmed that treatment with either the alpha-1 adrenergic receptor antagonist or the anti-muscarinic agent inhibits the increase of urinary ATP in patients with bladder dysfunction such as BPH or OAB.

It is known that bladder epithelial cells express both muscarinic and alpha-1 adrenergic receptors, that these cells produce acetylcholine and ATP, and that afferent nerve terminals in the bladder express muscarinic and purinergic receptors (2, 20). Therefore, acetylcholine produced by bladder epithelial cells may activate epithelial cells in an autocrine fashion via their muscarinic receptors. When bladder epithelial cells are activated by a stimulus, these cells are thought to respond by producing acetylcholine and ATP. Then autocrine positive feedback activation via acetylcholine induces more ATP production, after which acetylcholine and ATP both activate afferent nerve terminals in the bladder and finally induce bladder overactivity. Recent studies have revealed that treatment by alpha-1 adrenergic receptor antagonist decreases ATP release from the bladder epithelium *in vitro* (9), while muscarinic agonists provoke ATP release from cultured bladder epithelial cells (14). Therefore, the inhibitory effect of alpha-1 adrenergic receptor antagonists and anti-muscarinic agents may be partly due to blockade of ATP release from the bladder epithelium.

In the present study, administration of the alpha-1 adrenergic receptor antagonist to BPH patients decreased LUTS and also decreased the urinary ATP/creatinine ratio, and improvement of LUTS (especially the IPSS-total) was greater in patients with a high baseline ATP level. The symptoms of our BPH patients differed depending on their baseline urinary ATP/creatinine ratio. The high ATP-BPH group mainly had urinary voiding symptoms (high IPSS and QOL scores), while the low ATP-BPH group mainly had urinary collecting symptoms. In male BPH patients, the urinary ATP level did not necessarily reflect the severity of OAB, probably because individual urethral resistance varies with the stage

Table 4 *Change of urinary ATP/creatinine ratio and LUTS after administration of an anti-muscarinic agent in high ATP-OAB group and low ATP-OAB group*

	High ATP-OAB group			Low ATP-OAB group		
	Before	After	*P*	Before	After	*P*
The number of cases	14			16		
Age (years)	71 ± 12			67 ± 6		
Urinary ATP/creatinine ratio (mol/mg × E-10)	26.7 ± 15.0**	16.2 ± 11.3	0.003	4.0 ± 2.4	5.0 ± 5.7	0.196
OABSS						
urinary frequency at daytime	1.0 ± 0.6	0.7 ± 0.7	0.020	0.7 ± 0.6	0.4 ± 0.5	0.028
urinary frequency at nighttime	2.2 ± 0.8	1.3 ± 1.1	0.001	1.8 ± 0.9	1.4 ± 1.2	0.028
urgency	3.4 ± 1.6	2.4 ± 2.2	0.001	3.2 ± 1.8	1.4 ± 1.6	0.002
incontinence	2.6 ± 2.2	2.1 ± 2.1	0.045	2.8 ± 2.1	0.7 ± 1.4	< 0.001
OABSS-total	9.2 ± 4.2	6.6 ± 4.8	< 0.001	8.4 ± 3.3	3.9 ± 3.5	0.001
IPSS						
empty	0.6 ± 1.3	0.4 ± 1.3	0.168	0.8 ± 1.6	0.6 ± 1.4	0.181
frequency	3.6 ± 1.2**	1.5 ± 1.7	< 0.001	1.8 ± 1.5	1.1 ± 1.5	0.068
intermittency	0.2 ± 0.4	0	0.041	0.3 ± 0.5	0.2 ± 0.4	0.167
urgency	2.5 ± 1.8	1.1 ± 1.3	< 0.001	2.4 ± 1.6	0.6 ± 0.8	< 0.001
weak stream	1.1 ± 1.8	1.0 ± 1.7	0.349	0.9 ± 1.7	0.5 ± 1.3	0.005
hesitancy	0.3 ± 1.1	0.4 ± 1.3	0.168	0.1 ± 0.3	0.1 ± 0.3	–
nocturia	2.4 ± 1.1	1.4 ± 1.2	< 0.001	1.8 ± 1.0	1.4 ± 1.2	0.027
IPSS-total	10.6 ± 6.5	5.7 ± 6.7	< 0.001	8.1 ± 3.5	4.6 ± 4.3	< 0.001
QOL score	5.9 ± 0.4***	3.7 ± 1.8	< 0.001	4.8 ± 0.8	2.9 ± 1.5	< 0.001

Mean ± SD

High ATP-OAB group: patients with a urinary ATP/creatinine ratio over 8.0 mol/mg × E-10 before treatment.

Low ATP-OAB group: patients with a urinary ATP/creatinine ratio under 8.0 mol/mg × E-10 before treatment.

**: $P < 0.01$, ***: $P < 0.001$, compared the baseline levels (before) between high ATP-OAB group and low ATP-OAB group.

of BPH and other factors. However, our results still suggested that patients with a high urinary ATP/creatinine ratio have high IPSS and QOL scores, and can expect more marked improvement of urinary voiding disorders with alpha-1 adrenergic receptor antagonist therapy. In female OAB patients, treatment with the anti-muscarinic agent also decreased LUTS and the urinary ATP/creatinine ratio, and improvement of LUTS (especially the IPSS-urinary frequency score) was greater for patients with a high baseline urinary ATP level. The pretreatment QOL score was also higher in the high ATP-OAB group than the low ATP-OAB group. These results suggest that patients with a high urinary ATP/creatinine ratio have high QOL score and can expect marked improvement of urinary frequency by treatment with the anti-muscarinic agent. Since women do not have a prostate gland, the urinary ATP level may directly reflect their bladder activity. In female patients, the urinary ATP/creatinine ratio increased with age. However, there was no significant difference in age between the high ATP-OAB group and the low ATP-OAB group or between normal female controls and female OAB patients. Therefore, there may not be much meaning to the relation between age and urinary ATP levels in female patients.

There was also a sex difference of urinary ATP levels. The urinary ATP/creatinine ratio was about 4 times higher in female controls than male controls and this ratio was also about 2 times higher in female OAB patients than male BPH patients. The reasons for this marked sex difference of the urinary ATP/creatinine ratio are unknown. It is not uncommon for OAB to be idiopathic in female patients, although OAB is usually due to BPH or neurogenic bladder in male patients. Therefore, females may have some essential factor that increases ATP release from the bladder epithelium, and this putative factor may be one of the causes of OAB in females. If the mechanism underlying the increase of ATP in females is determined, it may lead to new therapy for OAB.

ATP is a major neurotransmitter for both motor and sensory neurons in the peripheral nervous system (1, 19). Recent findings have supported the notion that epithelial tissues (including the urothelium) may have a role in sensation (5, 7). Activation by exposure to pressure, stretch, or hypoosmotic stimulation leads to the release of ATP from epithelial cells (7, 11). Although it is difficult to prove that urinary ATP is derived mainly from the bladder epithelium, prior investigations have demonstrated that ATP release from cultured epithelial cells is increased in patients with interstitial cystitis (17). Therefore, the urinary ATP level may be a potential marker of pathological bladder activity. However, urinary ATP is also influenced by bacterial infection and renal dysfunction (18), so it is necessary to exclude such factors.

In conclusion, there was a large sex difference of the urinary ATP/creatinine ratio. This ratio was 4 times higher in control females than control males, as well as 2 times higher in female OAB patients than male BPH patients. This finding may be important when considering the cause of female OAB. Moreover, improvement of LUTS by treatment with the alpha-1 adrenergic receptor antagonist or the anti-muscarinic agent could be related to decreasing the urinary ATP/creatinine ratio in patients with BPH or OAB. Therefore, the urinary ATP level can be used as a marker of pathologic bladder function.

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