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Tadalafil for male lower urinary tract symptoms (LUTS) improves endothelial function

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Abstract

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Methods: Tadalafil 5 mg was administered to 20 patients with prostatic hyperplasia for whom an α1 blocker was ineffective. Voiding symptoms and vascular endothelial function were investigated before and after 4 and 12 weeks of administration, using commercial tests for vascular function and vascular endothelial function.

Results: The subjects had a median age of 65 years old, a mean BMI of 24.2, and a mean prostate volume of 36.2 ml measured using transabdominal sonography. Voiding symptoms were significantly improved by tadalafil, based on the International Prostate Symptom Score (IPSS), QOL index, and overactive bladder symptom score ($P<0.05$). There were also significant improvements in vascular function (change of brachial-ankle pulse wave velocity (baPWV) from 1701 (before) to 1657 (4 weeks tadalafil) and 1525 (10 weeks tadalafil) cm/s ($P<0.05$)), and vascular endothelial function (change of reactive hyperemia index (RHI) from 1.36 to 1.56 and 1.89 ($P<0.05$)). The change in RHI was significantly correlated with IPSS, QOL index, and baPWV.

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Key words: blood flow, LUTS, reactive hyperemia index, tadalafil, vascular endothelium

Introduction

The main cause of lower urinary tract symptoms (LUTS) in men is bladder outlet obstruction, but factors such as aging, arteriosclerosis, nutritional status, sexual dysfunction, and metabolic syndrome are also involved in a complex way. Circulatory disorders in the pelvic organs, including urinary bladder ischemia, may also be causative, and LUTS and erectile dysfunction often occur prior to coronary artery disease in arteriosclerosis- and diabetes-associated peripheral arterial circulatory disorder. This is widely accepted based on the vascular size hypothesis, which indicates that when arteriosclerosis progresses, ED develops earlier than cardiovascular events because the penile artery controlling erection is thinner than the coronary artery[1]. Therefore, LUTS and erectile dysfunction can be regarded as systemic vascular lesions and as important risk factors for coronary artery disease.

An α1 receptor blocker is the first choice for drug treatment of prostatic hyperplasia inducing bladder outlet obstruction, but a phosphodiesterase type 5 (PDE5) inhibitor is also a treatment option. PDE5 inhibitors such as tadalafil were originally developed as drugs for erectile dysfunction (ED), and it has recently been reported that daily administration of tadalafil at a low dose improves LUTS[2,3]. The mechanism of action may involve relaxation of smooth muscle of the bladder neck over the prostate, improvement of pelvic blood flow, lowering of inflammation, and improvement of afferent neurotransmission[4]. And Morelli et al. reported that tadalafil increases prostate tissue oxygenation[5,6]. PDE5 is distributed in pelvic organs such as the corpus spongiosum penis, urethra, and prostate, and also in the lung, heart, and vascular smooth muscle [7-9]. A PDE5 inhibitor has been reported to improve flow-mediated dilation (FMD), which is a measure of vascular endothelial function, through acting on vascular smooth muscle in the whole body [10].

Vascular function returns to normal when impairment is limited to endothelial disorder, but reversibility decreases as arteriosclerosis progresses. Thus, tadalafil may reduce the risk of cardiovascular events by improving vascular endothelial disorder in patients with LUTS as

a pre-symptom prior to development of cardiovascular events. Thus, we performed a clinical study of the effects of tadalafil on vascular function in Japanese patients.

Methods

The subjects were men aged ≥50 years old who were diagnosed with prostatic hyperplasia, did not respond to an α1 receptor blocker, and had an IPSS score ≥8 and a QOL index ≥2. Patients with a malignant tumor of the urinary tract, such as prostate cancer and urinary bladder cancer, those who had undergone surgery on the urinary tract, those with a suspected neurogenic bladder, or those in whom a PDE5 inhibitor was contraindicated were excluded from the study. Tadalafil 5 mg was administered once a day from April 2014, the date that administration of tadalafil in this patient population became possible in Japan. All patients continued oral medication with the α1 receptor blocker they were taking before the start of the study. There was no wash-out period for the α1 receptor blocker. The study was performed after approval by the Ethics Committee of Kawasaki Medical School Hospital (receipt number: 1418-4).

Evaluation items

Vascular endothelial function was evaluated before administration and after 4 and 12 weeks of tadalafil treatment. The primary endpoint was vascular function, and the secondary endpoints were voiding and erectile symptoms. The International Prostate Symptom Score (IPSS), QOL index, BPH Impact Index (BII), Overactive Bladder Symptom Score (OABSS), Sexual Health Inventory for Men score (SHIM), and Heinemann's aging male symptoms score (AMS) were used in evaluation.

Vascular function test

After resting for 10 minutes, vascular function was measured using a blood pressure/pulse

wave examination apparatus (Form ABI/PWV, Omron Colin, Komaki City, Japan) and a vascular endothelial function test apparatus (Endo-PAT2000, Itamar Medical, Caesarea, Israel). Using the Form ABI/PWV, blood pressure and the pressure pulse wave were measured in the bilateral upper arms and ankle joints, and the ankle joint/upper arm blood pressure ratio (ankle brachial index (ABI)) and brachial-ankle pulse wave velocity (baPWV) were determined [11]. This test requires 5 minutes and is a simple low-invasive procedure. ABI represents the brachial artery/ankle joint blood pressure ratio and is used to diagnose peripheral arterial diseases such as arteriosclerosis obliterans by estimating major arterial stenosis on the central side of the ankle joint. PWV is the speed of pulse wave propagation of arterial pulsation produced by blood ejection from the heart, and increases as arteriosclerosis progresses. Endo-PAT2000 is a blood flow-dependent vasodilatation reaction test that measures the reactive hyperemia index (RHI), similar to measurement of FMD[12]. Probes to measure fingertip pulse waves were attached to the fingertips of both hands. Measurements were made in a resting state for 5 minutes, followed by 5-minute avascularization and release, and then measurement for a further 5 minutes. Since vascular endothelial function can be evaluated noninvasively[13], the sympathetic nervous system has no influence and the test has high reproducibility. Thus, Endo-PAT2000 is approved as a vascular endothelial function test apparatus by the US FDA and European CE. RHI is also useful as a non-invasive measure of vascular endothelial function in vascular ED with a high risk of cardiovascular events[14].

Statistical analysis

Statistical analysis was performed using SPSS ver. 2, with a significance level of <5%.

Results

The 20 patients registered in the study had a median age of 65±5 years old, a mean BMI of 24.2±4.3, and a mean prostate volume was 36.2±6.8 ml measured using transabdominal

sonography. All patients were under medication with an oral α_1 receptor blocker before study initiation. Before the study, the mean IPSS was 16.9±4.1, QOL index was 4.7±0.3, and BII was 5.0±0.9, showing reduced scores (Table 1). There were no abnormalities in blood tests at the time of study initiation. The disease being treated was diabetes in 5 patients (25%), hypertension in 8 (40%), and hyperlipidemia in 6 (30%), and the course under oral drug treatment was favorable in all patients. In a vascular function test at the time of study initiation, ABI was normal, but PWV was 1,641±125 cm/s, showing a mild reduction, and the RHI of 1.91 was also mildly reduced. All other blood test items were normal and the free testosterone level was also normal.

Subjective and objective findings for voiding symptoms significantly improved after tadalafil administration compared with those before administration, and erectile symptoms also significantly improved. Regarding vascular function, there was no change in ABI, but PWV and RHI significantly improved (Table 2). These findings show that tadalafil can improve arteriosclerosis by improving vascular endothelial function.

Correlation coefficients of changes in RHI after administration for 12 weeks with each measured item were investigated to identify factors influencing improvement of RHI. Significant correlations were found with IPSS (total, voiding subscale), QOL index, and PWV; i.e., RHI improved in patients with mild impairment of IPSS and QOL before administration (Table 3, Fig 1a, 1b).

Discussion

Rosano et al. first reported that tadalafil 20 mg administered every other day improved FMD compared with a placebo group[10]. Subsequently, there have been many studies showing improvement of vascular endothelial function by PDE5 inhibitors. Shigemura et al. reported that PWV was improved by administration of sildenafil in Japanese patients with ED[15]. In this study, daily tadalafil 5 mg significantly improved vascular function. Since ABI was not

improved, tadalafil may not have major effects on large blood vessels. However, PWV and RHI improved, showing that vascular function improved when vascular reversibility was high. The action of vascular endothelium-impairing factors, such as oxidative stress, on normal blood vessels promotes vascular endothelial dysfunction, which then leads to arteriosclerosis. Cardiovascular events, such as myocardial infraction and stroke, occur as arteriosclerosis progresses. The reversibility of vascular endothelial dysfunction is high, with probable improvement of vascular function, but reversibility decreases as arteriosclerosis progresses. Therefore, therapeutic intervention is required in the vascular endothelial disorder stage to reduce the risk of cardiovascular events. The beneficial effect of tadalafil on vascular endothelial function may contribute to reduction of this risk.

Both relaxation of vascular smooth muscle and an increase in vascular endothelial cells may be associated with improvement of vascular endothelial function by tadalafil[16,17]. La Vignera et al. found an increased number of vascular endothelial cells after tadalafil administration[15], and these cells may accumulate in impaired regions of the vascular endothelium and repair these regions. In a basic study, an increase in vascular endothelial cells induced by a PDE5 inhibitor improved ischemic changes in rats[18].

Improvement of vascular function by tadalafil has previously been based on measurement of FMD. This is the gold-standard vascular endothelial function test for measuring reactive hyperemia of the brachial artery, but it has the disadvantage of requiring ultrasonography to visualize the radial artery, which requires time. In contrast, the Endo-PAT2000 system used in this study is simple, requires only a short time for measurement, and has high reproducibility. Since reactive hyperemia is measured in the fingertip arteriole, which is thinner than the radial artery used for measurement of FMD, earlier vascular endothelial dysfunction can be diagnosed. This is the study to show that improvement of vascular endothelial function by tadalafil can be measured using Endo-PAT2000.

An association between severity of LUTS and arteriosclerosis has been reported[19]. Thus,

LUTS are severe in patients with advanced arteriosclerosis. Since tadalafil improves dysuria and vascular endothelial dysfunction, the drug should be administered to patients with LUTS. RHI improved as IPSS decreased, indicating that arteriosclerosis is not advanced in patients with mild LUTS, in whom a more marked effect of tadalafil on blood vessels can be expected. Therefore, early tadalafil administration may be useful in patients with a high risk of cardiovascular events and LUTS.

Porst et al. reported that vascular endothelial function did not change in Endo-PAT2000 measurements in patients with ED treated with 5 mg of tadalafil in a randomized controlled study[20]. However, this study was performed at multiple institutions in Europe and included many patients who were highly sexually active despite having severe ED. In contrast, in our study, the SHIM score was low (9.5), which was due to the absence of sexual intercourse at the initiation of the study in 7 patients (35%). In severe ED, arteriosclerosis with low reversibility of vascular function has progressed, and in such cases tadalafil may not be expected to improve vascular endothelial function.

This study has limitations of not being placebo-controlled and including only 20 patients. Although However, improvement of vascular endothelial function by daily administration of tadalafil 5 mg in Japanese subjects was demonstrated using Endo-PAT2000. There has been no large-scale clinical study on improvement of vascular endothelial function by tadalafil, and therefore the data from this study have value. And there were limitations that the endpoint of our study was vascular endothelial function, and only changes in voiding symptoms after tadalafil administration were investigated. Therefore, no α1 blocker washout period was used before administration, and IPSS was not investigated when the α1 blocker was administered.

Peripheral circulatory disorder as a cause of urological diseases, dysuria and erectile dysfunction, develops before occurrence of cardiovascular events[21,22]. Incidences of dysuria and erectile dysfunction are likely to increase with aging of society, and diagnosis and

accurate treatment of vascular dysfunction may be important to maintain QOL of elderly people. Testing of vascular function is a major task, but several low-invasive simple tests have recently been developed. Performance of these tests and subsequent administration of tadalafil is recommended to improve QOL in patients with reduced vascular function.

In conclusion, measurements made with Endo-PAT2000 in this study showed that tadalafil improves vascular endothelial function, as well as LUTS and erectile dysfunction, with the effects on vascular endothelial function being particularly evident in patients with mild LUTS.

Conflict of Interest

None of the authors have a conflict of interest to disclose.

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Table 1. Background of the patients

Total Patients	N=20
Age(year), Median	65 (50-73)
BMI (kg/m^2)	24.2±4.3
Prostate Volume（ml）	36.2±6.8
Concomitant drugs	
α_1 blocker	7 (35%)
Tamsulosin	8 (40%)
Silodosin	5 (25%)
Naftopidil	2 (10%)
5αRI	
Dutasteride	2 (10%)
Comorbidity	
Diabetes	5 (25%)
Hypertension	8 (40%)
Hyperlipidemia	6 (30%)
IPSS（International Prostate Symptom Score）Total	16.9±4.1
IPSS Voiding subscale	11.6±2.9
IPSS Storage subscale	6.3±1.3
QOL index	4.7±0.3
BII（BPH impact index ）	5.0±0.9
SHIM score（sexual health inventory for men ）	9.5±1.2
AMS score	35.1±4.3
Uroflowmetry	
Qmax(ml/s)	9.3±2.1
PVR(ml/s)	26±4.6
Endothelial function	
ABI	1.13±0.12
baPWV	1641±125
Vessel Age（y）	72±10.2
RHI	1.91±0.4
Blood examination	
Tcho (mg/dl)	185±24
TG (mg/dl)	150±29
HDL (mg/dl)	48±9.6
LDL (mg/dl)	113±15
Free testosterone (pg/mL)	10.3±2.6

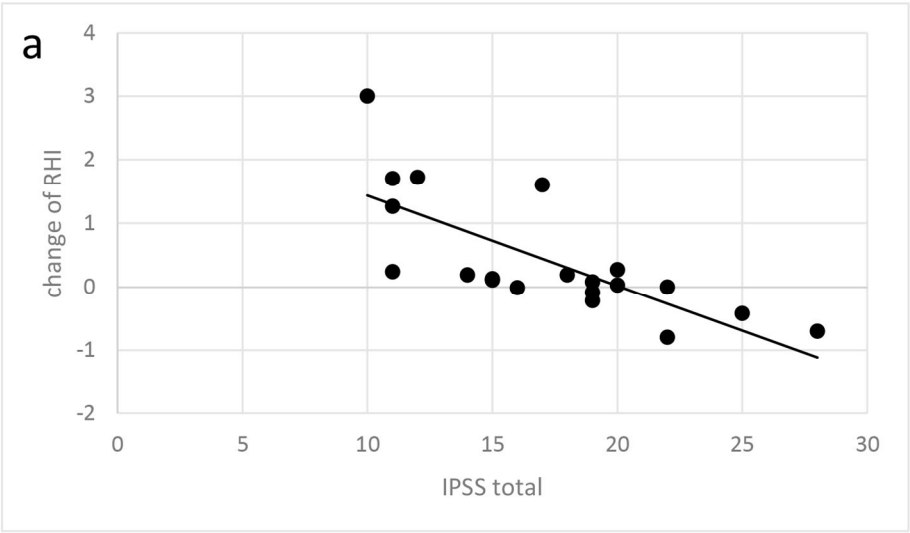
Table 2. Data before the study and after 12 weeks of administration of tadalafil

	baseline	12 weeks	p value
IPSS Total	17.1	10.4	<0.01
IPSS Voiding	11.6	6.2	<0.01
IPSS Storage	6.3	4.2	<0.01
QOL	4.7	3.1	<0.01
OABSS	4.3	3.1	<0.01
BII	4.95	2.95	<0.01
SHIM score	9.5	13.6	<0.01
AMS score	35.5	30.7	<0.01
Uroflowmetry			
Qmax	9.28	11.32	0.04
PVR	26	18.5	0.32
ABI	1.13	1.17	0.43
baPWV	1655	1480	<0.01
RHI	1.91	2.22	<0.01

Table 3. Correlation of change in RHI with items evaluated in the study.

	r	p
Age	0.23	0.52
Prostate Vol	0.34	0.41
IPSS Total	-0.72	<0.01
IPSS Voiding	-0.64	<0.01
IPSS Storage	-0.46	<0.01
QOL index	-0.75	<0.01
SHIM score	-0.42	0.04
AMS score	-0.3	0.09
Diabetes	0.51	0.01
Hypertension	0.44	0.04
ABI	0.11	0.32
PWV	-0.73	<0.01
PBI	-0.57	0.03

r = correlation coefficient



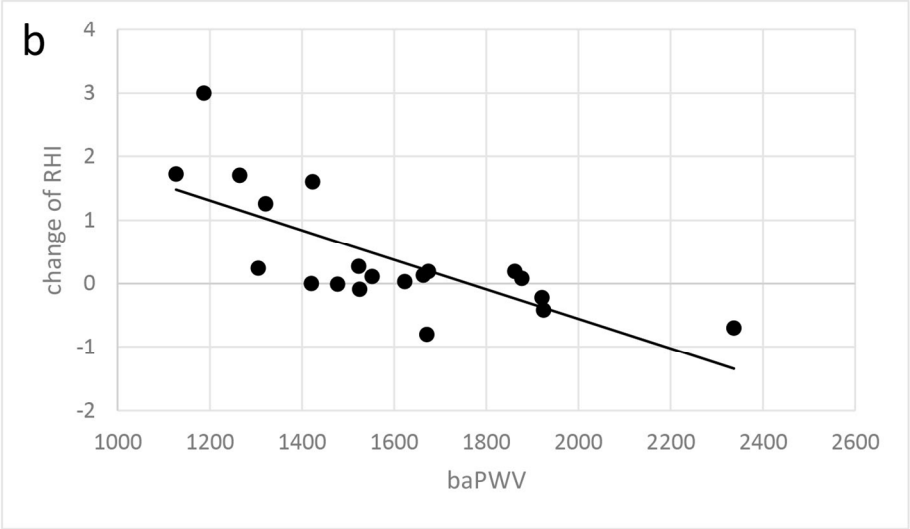


Fig 1. scatter plot about Correlation of change in RHI.
(a) Correlation of change in RHI and IPSS total (b) Correlation of change in RHI and baPWV.

127x159mm (300 x 300 DPI)