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The relationship between lower urinary tract symptoms associated with benign prostatic hyperplasia and erectile dysfunction: the role of autonomic hyperactivity

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Background/aim: To investigate whether autonomic nervous system (ANS) hyperactivity may be a potential cause for the relationship between lower urinary tract symptoms (LUTS) and erectile dysfunction (ED).

Materials and methods: Twenty-four patients were recruited for this study. Complete physical examinations, urine analysis, uroflowmetry, and postvoid residual urine volume (PVRU) analysis were performed. The potential impact of some factors such as hyperglycemia, obesity, and hyperlipidemia were analyzed. These values were correlated with the various symptom scores. We performed an electromyographic and an electrocardiographic evaluation. The alterations after treatment with 2 different alpha-blockers were also analyzed.

Results: The electromyographic and electrocardiographic assessments revealed a minimal increase in ANS activity and it did not change significantly after treatment ($P > 0.05$). After treatment, maximum flow rate increased and PVRU decreased significantly ($P < 0.001$ and $P < 0.001$, respectively); total and free testosterone levels increased significantly ($P = 0.0068$ and $P = 0.0071$, respectively). There was a statistically significant difference between the 2 treatment groups regarding the outcomes of the Danish Prostate Symptom Score questionnaire ($P = 0.047$).

Conclusion: This current study suggested that the effect of ANS hyperactivity is not the fundamental factor underlying the relationship between LUTS and ED.

Key words: Autonomic nervous system hyperactivity, benign prostatic hyperplasia, erectile dysfunction

1. Introduction

Lower urinary tract symptoms (LUTS) and erectile dysfunction (ED) are highly prevalent in aging men (1,2). A cross-sectional study evaluating the prevalence of LUTS over the age of 40 years revealed that its prevalence in elderly Turkish men is fairly high and increases with age (3). Because the number of men with LUTS associated with benign prostatic hyperplasia (BPH) and ED continues to increase, it is important to understand this disease complex. Both disorders have major impacts on the quality of life and socioeconomic implications, and both are projected to increase because of demographic changes (4). The hypotheses that have been proposed to understand the relationship between ED and LUTS are as follows: 1) increased Rho-kinase activation (5), 2) nitric oxide synthase (NOS)/nitric oxide (NO) level decrease or alteration (6), 3) atherosclerosis affecting the pelvis (7),

and 4) autonomic nervous system (ANS) hyperactivity (8). In a previous study, an association was shown between autonomic neural input to the prostate and prostatic growth in rats, such that the absence of autonomic neural input resulted in regression of the gland (9). These findings were supported by other animal studies using a strain of rats (spontaneously hypertensive rats) that develop increased autonomic activity, prostate hyperplasia, and erectile dysfunction (8,10,11). The ANS hyperactivity hypothesis has been further supported by epidemiologic studies (12,13).

The aim of this clinical study was to evaluate this association in detail in a consecutive series of men referred to our out-patient clinic in a predetermined time period. Our hypothesis was that ANS hyperactivity, especially sympathetic nervous system overactivity, might be a potential cause for the relationship between LUTS and

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sexual dysfunction. We analyzed the potential causes for the relationship between LUTS associated with BPH and ED and the effects of several variables (serum free and total testosterone levels, blood lipids, blood glucose level, calculations of the weight and waist), as well as the effect of autonomic hyperactivity. The alterations after treatment with 2 different alpha-blockers (tamsulosin, 0.4 mg/daily and alfuzosin, 10 mg/daily) were also analyzed.

2. Materials and methods

2.1. Patients and study protocol

Twenty-four consecutive patients were recruited for our study. The study was approved by the local ethics committee and all of the patients gave informed consent. The inclusion criteria for the study were men with moderate or serious LUTS associated with BPH [they had an International Prostate Symptom Score (IPSS) of >8], with a large prostate as identified by digital rectal examination and ED [International Index of Erectile Function-5 (IIEF-5) score of <21]. The patients were divided into groups for ED severity according to IIEF-5 score (mild, moderate, severe). The exclusion criteria were: 1) any prior medical or surgical intervention for BPH; 2) phenylephrine, pseudoephedrine, imipramine, or anticholinergic or cholinergic medication before or during the investigation; 3) any clinically significant renal or hepatic impairment or serious cardiovascular disease; 4) any suspicion of prostate cancer, either clinically or by prostate-specific antigen (PSA) levels; 5) any known neurological diseases affecting the central or peripheral nervous systems, such as multiple sclerosis; 6) serious diabetes mellitus for a long period of time with poor glycemic control, which may affect the innervation of the prostate, penis, and the bladder by peripheral neuropathy. Insulin resistance, without the presence of overt diabetes mellitus, has also been shown to impair the response to the alpha-blocker therapy in men with BPH (14).

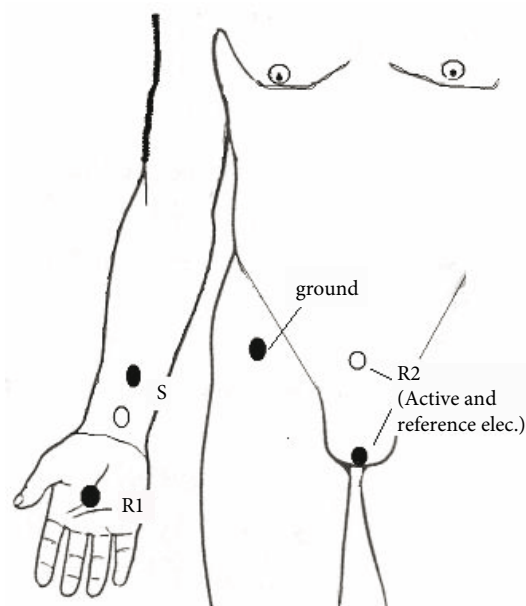
A complete physical examination, including digital rectal examination, urine analysis, uroflowmetry, and postvoid residual urine (PVRU) volume analysis for all patients, was performed at baseline. Serum free and total testosterone levels, and free and total PSA levels, were measured for the baseline evaluation of ED and BPH. The potential impacts of some factors frequently associated with increased sympathetic activity, like hyperglycemia, abdominal and total obesity, and hyperlipidemia, were also analyzed by measurement of serum lipid levels, blood glucose levels, and weight and waist calculations of the patients. These values were correlated with the various symptom scores, maximum flow rate (Qmax), and PVRU volume.

Patients were informed about the importance of diet and exercise on the sexual functions at baseline and at each

visit. To evaluate the autonomic activity circumstances, we performed an electromyographic assessment by amplitude and latency measurements of genitofemoral and peripheral nerves for assessment of local (genitourinary) and peripheral ANS activity (Figure 1). Additionally, an electrocardiographic evaluation was performed to assess heart rate during rest and hyperventilation. The RR intervals were calculated on the electrocardiogram, which was performed during rest and hyperventilation to assess the central ANS activity. Patients were also evaluated by the IPSS, IIEF, Danish Prostate Symptom Score Sex (DAN-PSSsex), and Aging Males' Symptoms (AMS) scale questionnaires. After baseline assessment, patients were randomly divided into 2 different treatment groups (tamsulosin, 0.4 mg/daily and alfuzosin, 10 mg/daily; 12 patients for each group). Patients were reassessed at the third and sixth months from baseline for alterations after treatment with alpha-blockers. At visits 2 and 3, we also performed physical examinations and other laboratory investigations.

2.2. Statistical analysis

Statistical analysis was performed using SPSS 16.0 for Windows (SPSS Inc., Chicago, IL, USA). Data were presented as mean \pm standard deviation for continuous variables. We used the chi-square test, Student's t-test,



S: Electric stimulation

R1: Upper extremity SSR record area

R2: Genitofemoral SSR record area

Figure 1. Electromyographic assessment of peripheral and genitofemoral nerves.

repeated measures ANOVA, the Bonferroni test, and covariation analysis. The alterations after treatment were investigated by repeated measures ANOVA and Bonferroni test. Covariation analyses especially revealed the relationship between laboratory findings before and after alpha-blocker treatment. Differences were considered to be significant at $P < 0.05$.

3. Results

A total of 24 consecutive men with LUTS and sexual dysfunction were recruited for our study. None of the patients discontinued the treatment due to side effects during the follow-up period. The mean follow-up period was 7.2 (6–18) months. The demographic data of the 2 treatment groups were comparable (Table 1). Multivariate analysis revealed that there was an objective negative correlation between increasing body weight and waist measurements and erectile function ($P < 0.001$). Furthermore, in the category of the objectively recorded data for LUTS associated with BPH and ED, we observed a negative correlation between free testosterone levels and weight and waist circumference measurements ($P = 0.02$)

(Table 2). Fasting blood glucose level was normal in all patients initially.

After treatment with 2 different alpha-blockers, of the objective data for LUTS, Qmax increased and PVRU volume decreased significantly ($P < 0.001$ and $P < 0.001$, respectively). The total and free testosterone levels increased significantly ($P = 0.0068$ and $P = 0.0071$, respectively). As all patients were informed about the importance of low dietary lipid intake and exercise, serum lipid levels of all patients showed a marginal decrease at follow-up. We observed a similar change in weight and waist circumference measurements at the second and third visits ($P > 0.05$). The PSA levels did not change significantly at follow-up and we did not determine any clinical signs of prostate cancer in any patients during the second or third visits.

The evaluation for ANS activity at baseline by electromyographic assessment of peripheral and genitofemoral nerves by amplitude and latency measurements for local and peripheral responses revealed a minimal activity increase in the sympathetic nervous system. On reassessment after treatment with alpha-

Table 1. Demographic data of the patients at baseline.

	Age (years)	IPSS score	IIEF score	Weight (kg)	Waist circumference (cm)	Total PSA level (ng/mL)	Qmax (mL/sec)	PVRU (mL)
Group 1 (alfuzosin)	57.4 ± 7.6	15.5 ± 4.4	14.3 ± 3.7	79 ± 11.6	99.5 ± 7.8	1.9 ± 1.5	12.4 ± 6	69.1 ± 67
Group 2 (tamsulosin)	57 ± 6.5	16.7 ± 4.7	14.1 ± 3.5	80.6 ± 8.4	99.6 ± 6.6	1.6 ± 1.3	13.7 ± 4.2	1.6 ± 43.4

Table 2. The changes in mean questionnaire scores and laboratory findings before and after alpha-blocker treatment.

	Alfuzosin			Tamsulosin		
	Before treatment	3rd month	6th month	Before treatment	3rd month	6th month
Total testosterone (ng/mL)*	5.9	6	6.3	5.9	6.8	6.7
Free testosterone (ng/dL)*	7.5	9.2	11.7	9.5	10	11.3
Qmax (mL/s)*	12.4	13.3	14.7	13.7	15.8	16.7
PVRU (mL)*	69.1	44.1	18.3	51.6	25	8.3
IPSS score	15.5	12.5	10.4	16.7	13.9	12.6
DAN-PSSsex* score	2.6/1.7/1.1	2.3/1.8/1	1.5/1.5/0.9	2/1.8/1.3	1.5/1.5/1.1	1.8/1.5/1
IIEF score	14.3	15.8	17.6	15.1	17.4	18
AMS score	29.5	26.3	24.8	33.8	30.5	29.1

*: $P < 0.05$.

blockers at the third and sixth months of treatment, there was no significant alteration of ANS activity (Figure 2; $P > 0.05$). Electrocardiographic assessment revealed a minimal increase in sympathetic nervous system activity at baseline, but this did not change significantly after alpha-blocker treatment (Figure 3; $P > 0.05$).

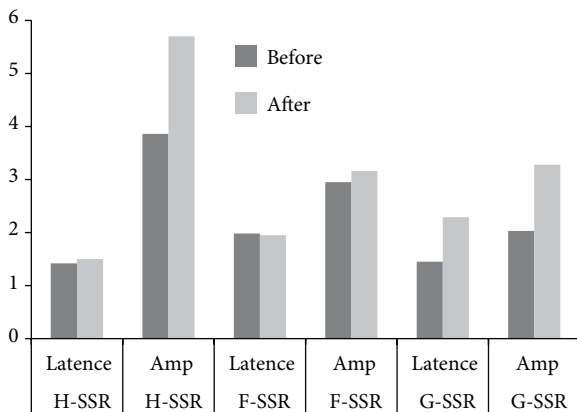
Regarding the questionnaires, IPSS values were negatively correlated with sexual function. At the baseline assessment before treatment with alpha-blockers, in the category of subjective variables for LUTS, multivariate analysis revealed a negative correlation between IPSS and IIEF scores ($P < 0.01$; Table 2). Two of the participants had severe (group A), 14 had moderate (group B), and 8 had mild (group C) ED at baseline. After treatment with alpha-blockers, IPSS decreased and IIEF scores increased significantly ($P < 0.05$). The changes in IIEF scores were similar in groups A, B, and C ($P > 0.05$). Severe LUTS

was also associated with high AMS scores (Table 2). After treatment with alpha-blockers, the IPSS, DAN-PSSsex, and AMS scale scores decreased and IIEF scores increased for all patients. There was a statistically significant difference between the 2 treatment groups regarding the outcomes of the DAN-PSSsex questionnaire due to the side effects of tamsulosin on ejaculatory function ($P = 0.047$).

4. Discussion

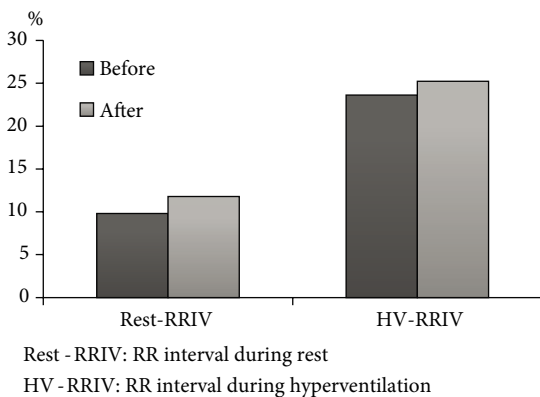
LUTS and ED are common and bothersome problems in aging males. It has been proposed that there might be a relationship between these clinical conditions. The 2 most important theories suggest that the relationship might have a direct pathophysiological basis, perhaps mediated by the sympathetic nervous system, or that the relationship might be psychological, such that the bother associated with urinary symptoms results in impaired sexual function (15,16). ANS hyperactivity is one of the hypotheses used to clarify the relation between LUTS and ED. This current study demonstrated that there is not a significant correlation among LUTS, sexual function, and ANS activity.

The Multinational Survey of the Aging Male (MSAM-7) (15), one of the largest population-based studies about aging males, evaluated the association between LUTS and male sexual dysfunction, and the effects of age and other comorbidities on these conditions, in 12,815 men in the United States and some European countries. The results of this study strengthened the current data about relationships between LUTS and sexual dysfunction in men, independent of the effects of age, comorbidities, and various habitual factors. In multivariate analyses that controlled for age, medical comorbidities (diabetes, hypertension, cardiac disease, and hypercholesterolemia), tobacco use, alcohol consumption, age, and the severity of LUTS were independent risk factors for both ED and ejaculatory dysfunction. A population-based study derived from a cross-sectional health survey demonstrated the high prevalence of LUTS and ED and their association (13). In this study, the potential impact of some factors frequently associated with increased sympathetic activity, like hyperglycemia, obesity, hypertension, and hyperlipidemia, were also analyzed by measurement of serum lipid levels, fasting glucose, body mass index, and blood pressure. Even though LUTS and ED are often associated with each other, total calorie intake, alcohol consumption, obesity, waist/hip ratio, diastolic blood pressure, presence of diabetes, and hypertension did not individually predict clinical BPH. Some epidemiological studies suggested that there may be a relationship between sympathetic overactivity and LUTS severity (12,13). However, these studies did not control for extrinsic factors that could potentially influence ANS activity, except for the study evaluating the effect of



H-SSR: Sympathetic skin responses from hand
 F-SSR: Sympathetic skin responses from foot
 G-SSR: Sympathetic skin responses from genitofemoral nerve

Figure 2. Latency (ms) and amplitude (mV) measurements of peripheral and genitofemoral nerves for all patients before and after alpha-blocker treatment.



Rest - RRIV: RR interval during rest
 HV - RRIV: RR interval during hyperventilation

Figure 3. Cardiac RR interval changes of all patients before and after alpha-blocker treatment.

ANS activity on the relationship between LUTS and ED by McVary et al. (16).

The assessment of sympathetic skin responses (SSRs) is a sensitive measurement of autonomic activity. In several reports, the effects of diabetes on autonomic activity were specifically investigated by SSR (17,18). The loss of potentials from the hand and/or foot is often regarded as a pathological sign of autonomic-sympathetic neuropathy. Earlier detection of sympathetic involvement of autonomic neuropathy seems to be possible in 2 ways. First, using SSRs can reveal the reduction of the amplitude and changes in latency in the extremities (18). Changes in latency and reduction of amplitudes have been recognized as initial signs of autonomic-sympathetic neuropathy (17–19). In the present work, we revealed that the genital and peripheral SSRs are easily obtained from subjects with LUTS and ED to assess the ANS activity. The assessment of ANS activity by SSRs did not reveal a significant activity increase in our cohort. One of the most fundamental functions of the ANS in humans is the maintenance of adequate heart rate during rest and activity. We evaluated RR interval variation during deep breathing

and rest to exploit this main function of the ANS. This electrocardiographic evaluation also did not suggest any significant ANS activity increase in patients with LUTS and ED. One of our limitations for the present study is the small number of subjects for each treatment group. The assessment of orthostatic control of vascular tone is also a sensitive measure of overall autonomic activity (20). The assessment of blood pressure as a considerable function of ANS could also be correlated with other measurements to evaluate ANS activity. Furthermore, this work only included patients applying for medical treatment for LUTS associated with BPH.

In conclusion, the current study suggested that the effect of an increase in ANS activity is not the fundamental factor underlying the relationship between LUTS and ED. The other hypotheses used to clarify the association between LUTS and ED, such as pelvic atherosclerosis, alpha-adrenergic receptor imbalance, decrease of NOS/NO in the endothelium, or increased Rho-kinase activation, might be more significant pathophysiologic mechanisms. There is a need for more prospective and randomized controlled studies.

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