Scandinavian Journal of Urology and Nephrology

ISSN: 0036-5599 (Print) 1651-2065 (Online) Journal homepage: http://www.tandfonline.com/loi/isju19

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A Comparison of Four Different α1-Blockers in Benign Prostatic Hyperplasia Patients with and without Diabetes

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(Submitted August 12, 2003. Accepted for publication April 14, 2004)

Scand J Urol Nephrol 38: 391–395, 2004

Objective: The aim of this study was to evaluate the intensity of lower urinary tract symptoms in patients with benign prostatic hyperplasia (BPH) with and without diabetes. We also determined whether α1-blockers improve subjective and objective symptoms similarly in these patients.
Material and Methods: The study subjects comprised 281 patients (60 with diabetes and 221 non-diabetics with clinically diagnosed BPH) who were treated with α1-blockers (doxazosin, terazosin, alfuzosin and tamsulosin). The international prostate symptom score (IPSS), bother score, maximum flow rate (Qmax) and post-void residual urine volume (PVR) were determined at baseline and after treatment for a minimum of 6 months.
Results: Diabetic patients had a lower baseline Qmax than non-diabetics ($p < 0.001$), while the IPSS, bother score and PVR did not differ significantly between the two groups. After treatment with α1-blockers, lower urinary tract symptoms improved significantly. The improvement rates of the IPSS and bother score were significantly higher in the diabetic patients than in the non-diabetics ($p < 0.01$). The relationship between the duration of diabetes and the effect of α1-blockers on IPSS, bother score, Qmax and PVR was not statistically significant ($p > 0.05$).
Conclusions: The voiding function of the bladder may be more affected by diabetes than the storage function in patients with BPH. Treatment with α1-blockers appears to be useful for diabetic patients with BPH and its effectiveness is not altered by the duration of diabetes.

Key words: benign prostatic hyperplasia, α1-blockers, diabetes mellitus, lower urinary tract symptoms.

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Lower urinary tract symptoms (LUTS) suggestive of symptomatic benign prostatic hyperplasia (BPH) are very common in elderly men. Approximately 25% of men aged >40 years suffer from LUTS, including a reduced maximum flow rate (Qmax) and an increased post-void residual urine volume (PVR) (1, 2). Although the underlying pathophysiology is different, diabetes can also cause LUTS such as a lower Qmax without bladder outlet obstruction and an increased PVR related to bladder dysfunction (3, 4).

The prevalence of both diabetes and BPH rises with age and a possible association between the two conditions has been debated for more than three decades (5–7). This association may also be important therapeutically and α1-blockers are recommended as the main pharmacological treatment for patients with BPH presenting with LUTS (8–10). Until recently, it has been reported that the α1-blocker tamsulosin appears to reduce LUTS and is similarly well tolerated in BPH patients with or without diabetes (11). To date, with the exception of tamsulosin, the effect of α1-blockers such as doxazosin, terazosin and alfuzosin in diabetic patients with BPH has not been reported.

In this study, we evaluated the intensity of LUTS in BPH patients with and without diabetes. We also determined whether the α1-blockers doxazosin, terazosin, alfuzosin and tamsulosin improved subjective and objective symptoms similarly in BPH patients with and without diabetes.

MATERIAL AND METHODS

A retrospective review of 281 newly diagnosed patients with LUTS suggestive of BPH who were treated with α1-blockers in our department between March 1999 and December 2001 was undertaken. Our clinic is a university hospital and all patients are self-referrals. Treatment consisted of 4 mg doxazosin daily, 5 mg terazosin daily, 2.5 mg alfuzosin 3 times daily or 0.4 mg tamsulosin daily. Concomitant diabetes in 60 patients was determined from medical histories based on a specific question in the case record forms.

 ISSN 0036–5599
DOI 10.1080/00365590410015678

Therefore, the patients with BPH included in the study were divided into two groups: 221 non-diabetic patients and 60 patients with diabetes mellitus.

In order to evaluate an association between diabetes and BPH symptoms, all patients were investigated initially by means of assessment of symptoms and determination of the bother score according to the Turkish validation of the international prostate symptom score (IPSS) (12), Qmax, PVR and prostate volume. Patients eligible for inclusion were men aged $\geq$50 years with IPSS $\geq$8 and bother score $\geq$3, Qmax $\leq$15 ml/s, prostate volume $\geq$30 cm^3 and PVR $<$150 ml. Patients with prostate cancer, urethral stricture (history of previous urethral instrumentation, urethritis or trauma) or neurological disorders affecting lower urinary tract function or an indwelling catheter or those who had previously been treated either surgically or medically were excluded from the study. The IPSS and bother score were self-recorded. The patients voided a sufficient volume of urine ($>$150 ml) during uroflowmetry were included and the flow curves were read manually in order to avoid artefacts. PVR was determined by means of transabdominal ultrasonography. Prostate volume was measured by means of transrectal ultrasonography and calculated using the formula for an ellipsoid: 0.53$\times$height$\times$length$\times$width. The assessment and follow-up schedule was standardized and was similar to that for BPH patients treated with α1-blockers at our clinic. The patients were treated for a minimum of 6 months with one of the α1-blockers. The last follow-up session was chosen for evaluation and those patients who experienced side-effects causing early discontinuation of treatment were not included in the evaluation. After treatment, the mean changes in the IPSS, bother score, Qmax and PVR were compared between the diabetic and non-diabetic patients.

Following basic descriptive statistics, the patient data were analysed using Wilcoxon's test and the Mann–Whitney U-test. In addition, the relationship between the duration of diabetes and the effect of treatment on symptoms was evaluated using Pearson correlation analysis. $p < 0.05$ was considered statistically significant.

RESULTS

Baseline data for the patients are shown in Table I. Diabetic patients had a lower Qmax than non-diabetics ($p < 0.001$) (Table I). As shown in Table II, according to the initial and subsequent parameters for the patients treated with the different types of α1-blocker there was no significant difference among the groups ($p > 0.05$), and in both diabetics and non-diabetics the α1-blockers significantly improved the IPSS, bother score, Qmax and PVR when compared with baseline values ($p < 0.001$). The improvement rates of the IPSS and bother score were significantly higher in the diabetic patients than in the non-diabetics ($p < 0.01$) (Table III, Fig. 1). The improvement rates of the parameters were the same for all the α1-blockers ($p > 0.05$). In terms of drug-related side-effects, no significant difference was found between the diabetics and non-diabetics ($p > 0.05$) (Fig. 2). All of the diabetic patients had type 2 diabetes, and the mean duration of diabetes was 11.5 ± 6.82 years. The relationship between the duration of diabetes and the effect of treatment with α1-blockers on the IPSS, bother score, Qmax and PVR was not statistically significant ($p > 0.05$) (Table IV).

DISCUSSION

BPH, as manifested by its associated LUTS, is a common and progressive clinical condition in older men (13). More than 50% of men aged $>$60 years will have LUTS, including a reduced Qmax and an increased PVR (1, 2). Although the underlying pathophysiology is different from that of BPH, long-standing diabetes can cause bladder dysfunction resulting in LUTS and the number of patients with diabetes is increasing with age. It has been shown that bladder dysfunction in diabetics is characterized by an impaired sensation of fullness, impaired bladder contractility and increased PVR as a result of the sensory and

Table I. *Baseline data and follow-up period of the patients with and without diabetes*

Characteristic	Diabetics (n = 60)	Non-diabetics (n = 221)
Age (years)	61.85 (50–80)	60.00 (50–85)
Follow-up (months)	13.25 (6–27)	11.52 (6–28)
IPSS	15.40 (8–33)	14.43 (5–34)
Bother score	3.51 (3–6)	3.34 (3–6)
Qmax (ml/s)	10.95* (5–15)	12.59 (5–15)
Prostate volume (cm^3)	36.90 (30–60)	36.08 (30–65)
PVR (ml)	58.56 (0–140)	44.62 (0–145)
Prostate-specific antigen level (ng/ml)	2.14 (0.4–8)	2.12 (0.6–8.6)

* $p < 0.001$ compared with non-diabetics.

Table II. *Results of α1-blocker treatment in the patients with and without diabetes. The mean values are given*

		IPSS*		Bother score*		Qmax*		PVR*	
α1-Blocker	*n*	Baseline	Later	Baseline	Later	Baseline	Later	Baseline	Later
Terazosin									
Non-diabetics	63	14.5	10.9	3.4	2.1	12.6	15.4	35.3	16.5
Diabetics	16	16.4	9.2	3.9	2.2	11.4	14.9	45.9	16.8
Doxazosin									
Non-diabetics	48	15.4	12.1	3.5	2.3	12.2	14.8	59.3	16.6
Diabetics	14	15.5	7.2	3.4	2.1	10.7	12.8	81.2	35.3
Alfuzosin									
Non-diabetics	42	13.1	9.4	3.3	2.1	11.3	14.1	29.7	12.7
Diabetics	13	12.9	6.5	2.7	1.5	10.2	13.8	41.4	16.4
Tamsulosin									
Non-diabetics	68	13.1	10.1	2.9	2.2	13.2	15.5	49.4	15.1
Diabetics	17	15.6	8.6	3.6	2.2	11.1	14.1	69.6	29.5
Total									
Non-diabetics	221	14.4	11.3	3.3	2.2	12.5	15.2	44.6	15.8
Diabetics	60	15.4	7.93	3.5	2.1	10.9	13.9	58.5	23.8

* Significant difference in parameters between baseline and later ($p < 0.001$).

autonomic nerve dysfunction induced by diabetic neuropathy (3, 4).

Because the prevalences of both diabetes and BPH rise with age, comorbidity between diabetes and BPH has been debated over the last few decades (5–7). In the present study, we retrospectively evaluated a group of patients treated with one of four α1-blockers (doxazosin, terazosin, alfuzosin and tamsulosin) at our clinic who underwent a standardized assessment and follow-up schedule. Our patients were clinically diagnosed with BPH and were recruited based on BPH symptoms similar to those reported in most of the previous studies (7, 11). In order to clarify whether the association between BPH and diabetes may cause more severe LUTS, several studies compared the baseline data in diabetic and non-diabetic patients with BPH (7, 11). In a retrospective analysis of a large observational study, Michel et al. (11) demonstrated that diabetics had a significantly greater baseline IPSS and a smaller Qmax than non-diabetic patients (age-adjusted analysis). Diabetic patients were significantly older than non-diabetic controls in their study. In the present study, we did not find a significant age difference between diabetics and non-diabetics and one of the main advantages of our study is the fact that the data were obtained from patients at a single centre, giving the potential for greater homogeneity. The indication to start α1-blocker treatment at our clinic is consistent with the criteria of the International Consensus Committee on BPH (14). On the other hand, our patients were primarily referred to our outpatient department of urology because of LUTS suggestive

Table III. *Mean changes in the IPSS, bother score, Qmax and PVR*

		Mean change (%)			
α1-Blocker	*n*	IPSS*	Bother score*	Qmax	PVR
Terazosin					
Non-diabetics	63	24.8	33.7	25.1	57.5
Diabetics	16	42.8	42.2	31.6	76.6
Doxazosin					
Non-diabetics	48	19.6	29.6	24.36	83.7
Diabetics	14	52.9	42.6	17.9	62.8
Alfuzosin					
Non-diabetics	42	27.9	33.2	30.2	84.8
Diabetics	13	47.2	46.5	38.1	68.1
Tamsulosin					
Non-diabetics	68	21.9	19.8	21.1	78.7
Diabetics	17	43.9	40.5	27.9	70.6
Total					
Non-diabetics	221	23.5	29.9	24.9	72.9
Diabetics	60	46.5	42.5	27.7	69.4

* Significant difference in parameters between diabetics and non-diabetics ($p < 0.01$).

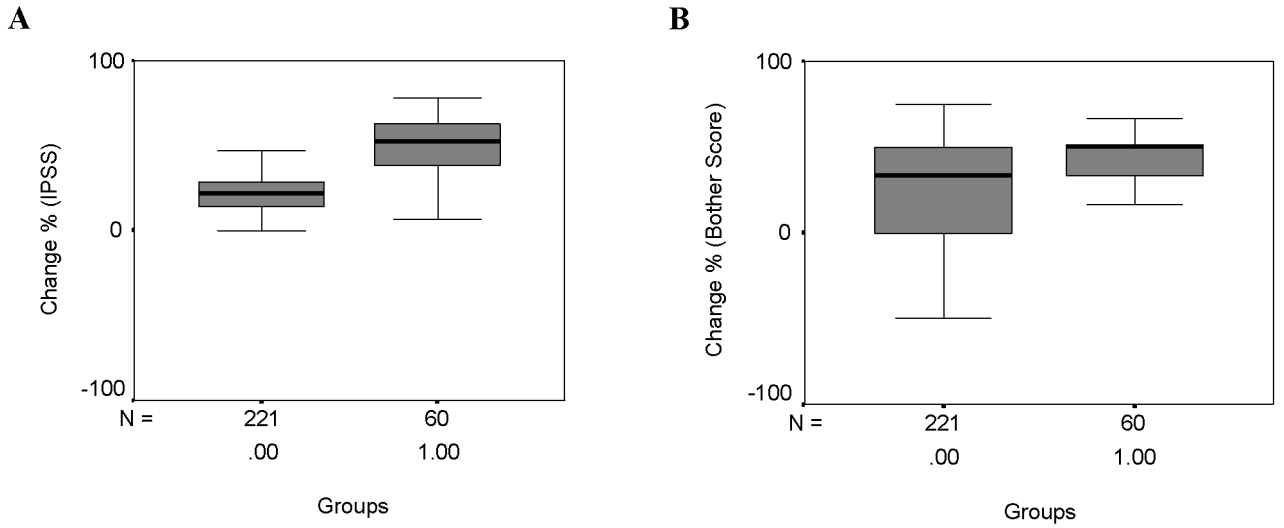

Fig. 1. Comparison of the improvement rates of (A) the IPSS and (B) the bother score in BPH patients treated with α1-blockers (".00" = diabetics; "1.00" = non-diabetics) ($p < 0.01$).

of BPH and the studied patients were only those selected for α1-blocker treatment. In other words, the limitation of our study is that our data were not generated in a population-based manner and the patients were deemed candidates for α1-blocker treatment because they had been clinically diagnosed with BPH and not because of diabetes. However, in previous studies on BPH and diabetes (5, 7, 11), patients were also recruited based on BPH symptoms and although this method of patient recruitment cannot exclude a certain selection bias it yields results that may be representative of patients seen in the urological office.

Although it may be expected that diabetic patients will have more severe LUTS than non-diabetics, we did not find any statistically significant difference in the baseline values of the IPSS and bother score between the two conditions, similar to the study reported by Boon et al. (7). In addition, we demonstrated that diabetic patients had a lower Qmax than non-diabetics, although PVR was similar in both groups. Our findings indicate that the voiding function of the bladder may be more affected by diabetes than the storage function. The previous study conducted by Michel et al. (11) has also supported our results of baseline Qmax and PVR in the patients; however, no significant differences were found between these parameters in the urodynamic evaluation performed by Boon et al. (7).

The underlying pathophysiology of diabetes and BPH is different; however, both conditions can cause similar symptoms, and this may also be important therapeutically. α1-Blockers are effective and are currently the first line of therapy for relieving the symptoms of BPH (10). More recently, it has been demonstrated that tamsulosin appears to reduce LUTS and is similarly well tolerated in BPH patients with or without diabetes (11). However, to our knowledge, the effect of α1-blockers such as doxazosin, terazosin and alfuzosin in diabetic patients with BPH has not been reported previously. It has been demonstrated that all α1-blockers have similar efficacy in terms of improving symptom scores and urinary flow rates in patients with BPH (15–17). In the present study, the dosages of the α1-blockers were suboptimal and no dosage changes were made. As expected, we found that doxazosin, terazosin, alfuzosin and tamsulosin significantly

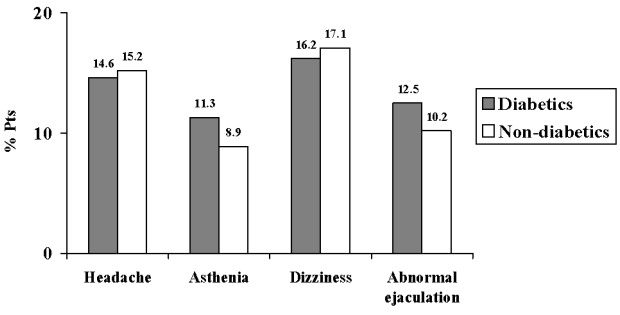

Fig. 2. Side-effects related to α1-blockers.

Table IV. *The relationship between the duration of diabetes and the effect of treatment on the parameters determined*

Parameter	*r*	*p*
IPSS	0.098	0.455
Bother score	0.044	0.741
Qmax	0.038	0.733
PVR	0.055	0.714

improved the IPSS, bother score, Qmax and PVR when compared with baseline values. Moreover, we found a similar incidence of side-effects in both diabetic and non-diabetic patients according to the retrospective records. Patients with side-effects causing early discontinuation of treatment were not included in the evaluation, because the time to follow-up of these patients was not 6 months. However, according to our retrospective records, the incidence of side-effects causing early discontinuation of treatment was similar in both diabetic and non-diabetic patients (15.6% vs 14.1%). Interestingly, we demonstrated that the improvement rates of the IPSS and bother score were higher in the diabetics than in those patients without diabetes. On the other hand, we did not find any difference in the improvement rates of Qmax and PVR between the patients with and without diabetes. It could be proposed that diabetes may affect bladder outlet resistance as a result of an alteration in the responsiveness of smooth muscle α1-adrenoceptors. To our knowledge, no studies have been reported on the urethral and/or prostatic α1-adrenoceptor function of diabetic animals and further experimental studies are required to test the hypothesis of an alteration of the function of these receptors in diabetes. LUTS in diabetic patients with BPH are partly due to diabetes and it becomes relevant to know whether these patients respond as well to α1-blocker treatment as patients without diabetes. Our data indicate that the α1-blockers doxazosin, terazosin, alfuzosin and tamsulosin have a more beneficial effect on subjective rather than objective symptoms in diabetics, when compared with non-diabetic patients with BPH. In addition, we demonstrated that the duration of diabetes does not alter the effectiveness of α1-blockers.

In conclusion, conflicting results have been reported regarding whether the combination of diabetes and BPH can cause more severe LUTS. The voiding function of the bladder may be more affected by diabetes than the storage function in patients with BPH. Treatment with α1-blockers would seem to have a greater effect on symptom scores and the bother score in diabetic patients. Our data indicate that doxazosin, terazosin, alfuzosin and tamsulosin appear to be effective also for diabetic patients with BPH; the effectiveness of this treatment modality is maintained and does not depend on the duration of diabetes.

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