Efficacy of Alfuzosin in Male Patients with Moderate Lower Urinary Tract Symptoms: Is Metabolic Syndrome a Factor Affecting the Outcome?

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Purpose: The present study was designed to compare the efficacy of alfuzosin therapy as an alpha-blocker in metabolic syndrome (MetS) and non-MetS patients with moderate lower urinary tract symptoms (LUTS).

Material and Methods: This prospective-observational study included male patients with obstructive voiding and had a moderate LUTS according to International Prostate Symptom Score (IPSS). Patients were divided into two groups: MetS and Non-MetS. Following the measurement of uroflowmetric parameters (maximum flow rate [Qmax], post-void residual volume [PVR], urine volume) and the determination of IPSS scores, the patients were initiated on alfuzosin 10 mg once daily for a period of 12 weeks. At the end of the therapy, treatment outcomes were determined based on uroflowmetric parameters and IPSS scores.

Results: 301 patients were included in the study (MetS: 160, non-MetS: 141). Pre-treatment uroflowmetric measurements and IPSS scores were similar in both groups. After the therapy, the median Qmax level increased from 12.80 (10.62-14.82) ml/s to 14.55 (12.00-16.60) ml/s in the MetS group and from 12.60 (8.60-14.60) ml/s to 15.70 (13.20-17.20) ml/s in the non-MetS group ($p < 0.001$ for both). Similar statistically significant changes were valid for PVR and IPSS. Post-treatment Qmax, PVR values and IPSS scores were higher in the non-MetS patients compared to MetS patients.

Conclusion: Although the non-MetS patients had greater benefit from the alfuzosin therapy compared to the MetS patients, alfuzosin is an effective alpha-blocker in the treatment of MetS patients with moderate LUTS. Based on these findings, it is tempting to consider that MetS might be a negative factor for benign prostate hyperplasia treatment.

Keywords: metabolic syndrome; benign prostatic hyperplasia; alfuzosin; lower urinary tract symptoms

INTRODUCTION

Benign prostate hyperplasia (BPH) is a common benign disease particularly in elderly men, arising from the transition zone of the prostate[1,2]. BPH often leads to lower urinary tract symptoms (LUTS) including urgency, straining to urinate, slow urinary stream, and intermittency[3]. Although its etiology remains unclear, BPH has been associated with chronic inflammation and metabolic syndrome (MetS) in numerous studies [1,4,6,7].

Metabolic syndrome (MetS) is an endocrinological disorder characterized by abdominal obesity, dyslipidemia, hyperglycemia, hypertension, and insulin resistance [5]. MetS has a wide variety of definitions and criteria [8]. One of these definitions was suggested by the International Diabetes Federation (IDF). According to the IDF definition, a diagnosis of MetS is made based on the presence of following criteria: enlarged waist circumference (with population-specific and country-specific criteria), elevated triglyceride, reduced high-density lipoprotein (HDL), increased blood pressure, and elevated blood glucose level[9].

Alpha-blockers are known as an effective and primary treatment for BPH[10]). Although these drugs have been shown to be a successful treatment option for BPH/LUTS, there are a limited number of prospective and controlled studies reporting on the effectiveness of these drugs in MetS patients[10-13].

The aim of this study was to compare the efficacy of alfuzosin therapy as an alpha-blocker in MetS and non-MetS patients with LUTS.

METHODS

Patient selection

The prospective-observational study included male patients aged 45-75 years who presented to Kayseri City Hospital Internal Diseases Polyclinic and Urology Polyclinic with the complaints of urination problems and had a total prostate volume (TPV) of 30-60 mL on transabdominal ultrasonography (USG) and a moderate

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Table 1. Demographic and clinical characteristics of the groups.

Variable	Patients with MetS (n=160)	Patients without MetS (n=141)	*p*
Age (years)	59.18 ± 7.53	59.38 ± 6.49	0.799
Body mass index (kg/m^2)	30.60 ± 4.10	24.70 ± 3.06	< 0.001
Waist circumference (cm)	111.00 (99.50-120.00)	84.00 (78.00-92.00)	< 0.001
Fasting blood glucose (mg/dL)	174.59 ± 72.54	74.88 ± 9.98	< 0.001
HbA1c %	8.14 ± 1.70	- -	
Creatinine (mg/dL)	0.92 ± 0.28	0.88 ± 0.18	0.900
HDL (mg/dL)	39.56 ± 11.98	42.67 ± 7.39	0.006
LDL (mg/dL)	115.50 ± 38.27	94.40 ± 18.68	< 0.001
Cholesterol (mg/dL)	184.72 ± 52.36	138.91 ± 23.09	< 0.001
Trygliceride (mg/dL)	197.00 (132.25-268.75)	156.00 (95.00-169.00)	< 0.001
Total prostate volume (mm^3)	46.85 ± 7.19	46.79 ± 6.94	0.939
Transitional zone volume (mm^3)	32.94 ± 7.69	33.13 ± 7.66	0.824
PSA (ng/ml)	0.95 (0.60-1.60)	0.90 (0.63-1.50)	0.848

HDL: High-density lipoprotein, LDL: Low-density lipoprotein, PSA: Prostate-specific antigen

(8-19 points) LUTS score according to International Prostate Symptom Score (IPSS). Exclusion criteria were as follows: an ongoing LUTS treatment, prior prostate surgery, post-void residual volume (PVR)>50 mL, mild or severe LUTS according to IPSS, an elevated prostate specific antigen (PSA) level, and use of drugs (anticholinergic, diuretic etc.) that could affect urinary functions. Additionally, diabetic and elderly patients with PVR >50 mL were excluded to rule out neurogenic bladder, and patients with a known neurological disease that could lead to neurogenic bladder were also excluded from the study. Study flow chart is shown in **Figure 1**.

Study protocol

Patients meeting the inclusion criteria were divided into two groups based on the IDF criteria: (I) MetS group and (II) Non-MetS group. In each patient, body height, weight, and waist circumference (WC) were measured during diagnosis. WC was measured using the standard method at a site 2 cm below the umbilicus. Additionally, fasting blood glucose, serum creatinine, PSA, HDL, low-density lipoprotein (LDL), serum cholesterol, and triglyceride levels were also measured in each patient. Patients that had a previous diagnosis of diabetes mellitus (DM) and the patients included into the MetS group additionally underwent glycolized hemoglobin (HbA1c) measurement. Each patient underwent uroflowmetry and also completed a self-administered IPSS questionnaire. Uroflowmetric measurements included maximum flow rate (Qmax), PVR, and urine volume. To avoid bias, uroflowmetry was repeated in patients with a bladder filling volume of <150 mL. TPV and transition zone volume (TZV) were calculated by transabdominal USG, using the following formula: Volume (mL) = width (cm) × height (cm) × length (cm) × 0.523. PVR was calculated, after voiding, using the following formula: PVR (mL) = width (cm) × height (cm) × length (cm) × 0.625. Blood glucose levels were measured in peripheral venous blood samples after 6-8 hours of fasting between 08.00 and 10.00 AM in each patient.

Following these procedures, the patients were initiated on alfuzosin 10 mg once daily for 12 weeks and were called for a follow-up visit. At the follow-up visit, the patients underwent uroflowmetry (Qmax, PVR, urine volume) and completed the IPSS questionnaire for a second time. The patients were also queried about the adverse effects of alfuzosin such as orthostatic hypotension, retrograde ejaculation, and allergic reaction. Pre- and post-treatment urine volumes were compared between the two groups.

International Diabetes Federation (IDF)

The IDF's definition included central obesity (defined as WC >94 cm) with ethnicity-specific values, plus two of the following: triglyceride ≥150 mg/dL, HDL cholesterol <40 mg/dL, blood pressure ≥130/85 mmHg, fasting blood glucose ≥100 mg/dL[5].

Statistical analysis

Data were analyzed using SPSS for Windows version 22.0 (IBM SPSS Inc., Armonk, NY, USA). Normal distribution of data was determined using Shapiro-Wilk test and histogram plots. Continuous variables were expressed as mean ± standard deviation (SD) or median (1st-3rd quartile). In independent groups, continuous variables with normal distribution were compared using Independent Samples *t*-test and continuous variables with nonnormal distribution were compared using Mann-Whitney U test. In dependent groups, continuous variables with nonnormal distribution were compared using Wilcoxon signed-rank test. A *p* value of < 0.05 was considered significant.

Ethical considerations: The present study protocol was

Table 2. Pre- and post-treatment urinary parameters.

		Patients with MetS (n=160)	Patients without MetS (n=141)	*p*
Pre-treatment	Qmax (ml/s)	12.80 (10.62-14.82)	12.60 (8.60-14.60)	0.286
	Urine Volume (ml)	260.00 (222.75-310.00)	260.00 (229.00-322.00)	0.374
	PVR (ml)	33.50 (25.00-40.00)	35.50 (25.00-42.00)	0.194
	IPSS	15.00 (13.25-17.75)	15.00 (13.00-17.50)	0.944
Post-treatment (12 weeks)	Qmax (ml/s)	14.55 (12.00-16.60)	15.70 (13.20-17.20)	0.045
	Urine Volume (ml)	250.00 (230.00-295.00)	250.00 (221.00-280.00)	0.432
	PVR (ml)	15.00 (10.00-20.00)	10.00 (0-10.00)	<0.001
	IPSS	13.00 (11.00-15.00)	10.00 (9.00-12.00)	<0.001

PVR: Post-voiding residual urine, IPSS: International prostate symptom score, MetS: Metabolic Syndrome

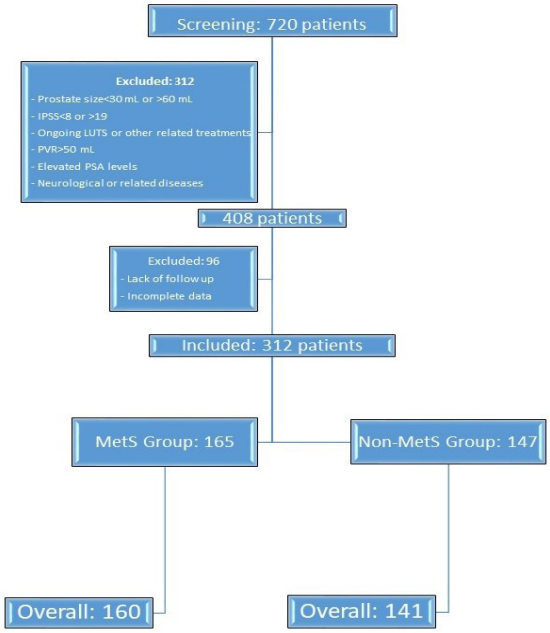

Figure 1. Study follow chart.

reviewed and approved by the Institutional Review Board of Erciyes University Faculty of Medicine (approval number: 2019/626). Informed consent was obtained by all subjects when they were enrolled.

RESULTS

The study evaluated a total of 312 patients that met the inclusion criteria. Of these, 11 patients were excluded from the study due to adverse events related to the treatment. As a result, a total of 301 patients were included in the study, of whom 160 patients were classified into the MetS group (Group I) and 141 patients were classified into the non-MetS group (Group II). The groups were similar with regard to mean age, TPV, TZV, and median PSA levels. However, WC, body mass index (BMI), and lipid profiles were higher in the MetS group compared to the non-MetS group (**Table 1**).

Comparison of pre-treatment urinary functions

Pre-treatment urinary parameters including Qmax, PVR, and urine volume were similar in both groups. Table 2 presents the comparison of pre-treatment levels measured in both groups.

Effect of alfuzosin therapy on Qmax values

After the 12-week alfuzosin therapy, the median Qmax level increased from 12.80 (range, 10.62-14.82) ml/s to 14.55 (range, 12.00-16.60) ml/s in the MetS group and from 12.60 (range, 8.60-14.60) ml/s to 15.70 (range, 13.20-17.20) ml/s in the non-MetS group ($p < 0.001$ for both). Although this increase was significant in both groups, after treatment, the Qmax of non-MetS patients were better than MetS patients ($p < 0.001$). **Table 2** presents the comparison of pre- and post-treatment levels measured in both groups.

Effect of alfuzosin therapy on PVR

The therapy resulted in a significant reduction in PVR values in both groups. The median PVR level decreased from 33.50 (range, 25.00-40.00) mL to 15.00 (range, 10.00-20.00) mL in the MetS group and from 15.00 (range, 13.00-17.50) mL to 10.00 (range, 9.00-12.00) mL in the non-MetS group ($p < 0.001$ for both). Moreover, although the pre-treatment PVR values were similar in both groups, the median post-treatment PVR value was significantly higher in the MetS group compared to the non-MetS group (15.00 [range, 10.00-20.00] mL vs. 10.00 [range, 0-10.00] ml) ($p<0.001$) (Table 2).

Effect of alfuzosin therapy on IPSS

A significant improvement was observed in the IPSS scores in both groups ($p < 0.001$), whereby the median pre-treatment IPSS scores in the MetS and non-MetS groups were 15.00 (range, 13.25-17.75) and 15.00 (range, 13.00-17.50) and the median post-treatment IPSS scores were 13.00 (range, 11.00-15.00) and 10.00 (range, 9.00-12.00), respectively ($p < 0.001$ for both). Additionally, these scores also indicated that the post-treatment IPSS of non-MetS patients were better than MetS patients (**Table 2**).

Moderate LUTS was diagnosed in all patients in both groups based on pre-treatment IPSS scores. However, based on post-treatment IPSS scores, mild LUTS was diagnosed in 6 (3.8%) patients in the MetS group and 31 (22%) patients in the non-MetS group ($p < 0.001$).

Alfuzosin safety: prevalence of adverse events

Two (1.2%) and 3 (1.8%) patients in the MetS group and 2 (1.4%) and 4 (2.7%) patients in the non-MetS group discontinued the therapy due to retrograde ejaculation and orthostatic hypotension and were excluded from the study, respectively. No other adverse events occurred in our patients. Moreover, no significant difference was found between the two groups with regard to the prevalence of adverse events ($p = 0.615$).

DISCUSSION

The most important finding of the present study was that both MetS and non-MetS patients with BPH and moderate LUTS benefited from an alfuzosin 10 mg therapy. However, the Qmax, PVR, and IPSS results indicated that the non-MetS group had greater benefit from this therapy and showed a greater reduction in symptoms compared to the MetS group.

Although the exact etiology of BPH remains unknown, MetS is known to play a role in the etiology of BPH and also to aggravate its symptoms[14,15]. Alpha-blockers are pharmacological agents, which have been shown to be effective in the treatment of BPH[16]. Additionally, the effectiveness of alpha-blockers in MetS has also been shown in several studies[10-12]. In a prospective study conducted in 2013, Lee et al. evaluated the effectiveness of doxazocin as an alpha-blocker in a total of 109 patients with BPH. In that study, all the patients received doxazocin 4 mg once daily for a period of 12 weeks and a total IPSS decrease of more than 4 points from baseline after 12 weeks of treatment was accepted as treatment success. The authors concluded that the presence of MetS had a significantly negative impact on the treatment success[10]. However, that study, unlike our study, involved patients with moderate to severe LUTS. Another prospective study that was conducted in 2014 evaluated the effectiveness of a prazosin 1 mg twice a day + finasteride 5 mg daily therapy for a 12-week period in a cohort of 100 patients that included 47 patients with MetS and 53 patients without MetS. The study reported that the patients with MetS

showed a 6-point decrease in IPSS score and the patients without MetS showed an 11-point reduction in IPSS score, implicating that the patients with MetS had less benefit from the BPH treatment[11]. Nevertheless, there are some other studies asserting the contrary[12,13]. A prospective, multicentric study that was conducted by Yoon et al. in 2015 evaluated the effectiveness of a 24-week tamsulosin therapy in a group of 92 patients comprising 39 patients with MetS and 53 patients without MetS and indicated that the therapy showed similar effectiveness in both groups[12]. However, the study presented different findings compared to those in the literature, which could be attributed to the inclusion of both male and female patients into the study and the wide age range of the patients (20-75 years). Literature reviews indicate that there are a limited number of studies investigating the effectiveness of alfuzosin in MetS patients and, to our knowledge, the study conducted by Altin et al. in 2015 is the only study reporting on the effectiveness of alfuzosin in MetS patients. The study evaluated the efficacy of a 12-week alfuzosin therapy in a group of 68 including 34 patients with MetS and 34 patients without MetS and indicated that the therapy showed similar effectiveness in both groups and also found that MetS is not a significant factor in the success of BPH treatment[13]. However, that study, unlike our study, only included patients with moderate LUTS and did not include patients with moderate to severe LUTS. In our study, the alfuzosin therapy led to a significant improvement in urinary parameters including Qmax and PVR in MetS and non-MetS patients with moderate LUTS. This improvement, however, was more limited in non-MetS patients compared to MetS patients and the findings also revealed that MetS may be a negative factor for the effectiveness of alfuzosin therapy. Accordingly, it can be asserted that the findings of our study are consistent with those reported by Lee et al.[10] and Cyrus et al[11].

Alfuzosin is a uroselective alpha-blocker that has been shown to be effective in BPH treatment[17-19]. A previous study evaluated the effectiveness of a 3-month alfuzosin therapy in a cohort of 1,051 patients and indicated that the therapy led to an improvement of 4 ml/sec in the Qmax value. The authors also noted that the IPSS score showed a 5.5-unit change after the therapy[17]. Another study evaluated the effectiveness of a two-year alfuzosin 10 mg therapy and reported that the IPSS score showed a 2.5-unit improvement after 6 months and a 6.5-unit improvement after the two-year period [19]. In our study, the three-month alfuzosin therapy led to an improvement of 3 ml/sec in the Qmax value and a 5-unit improvement in the IPSS score in non-MetS patients with BPH. These findings were consistent with those reported in the literature.

Of all patients in our study, 4 (1.3%) and 7 (2.3%) patients discontinued the therapy due to retrograde ejaculation and orthostatic hypotension, respectively. Although there are no studies in the literature comparing the adverse effects of alpha-blockers with regard to the presence of MetS, our findings indicated that the presence of MetS had no significant effect on the prevalence of adverse events in our patients. Debruyne et al. reported the prevalence of postural hypotension in patients receiving alfuzosin therapy as 0.6%. In the same study, however, no retrograde ejaculation was observed in none of the 358 patients included in the study [17]. A recent study evaluated the efficacy of alfuzosin therapy in patients undergoing expulsion of the stone and reported that retrograde ejaculation and orthostatic hypotension occurred in 2% of the patients each[20]. Another study evaluated the outcomes of 335 patients that completed a 7-day alfuzosin therapy 10 mg therapy and reported the prevalence of hypotension as 0.74% [21]. Based on these findings, it can be asserted that our findings are consisted with the literature.

Our study was limited in several ways. First and foremost, the study had a small patient population. Second, the study had no placebo group despite being an observational drug study. Third, the study had short follow-up periods and had no results regarding the response to long-term alpha-blocker therapy. Although the inclusion of patients with moderate LUTS alone could have produced more homogeneous and more reliable findings, these findings might be generalized to only a small patient population. Finally, the absence of hormonal parameters (e.g. testosterone) that are closely related to Mets and LUTS is an important limitation of our study.

CONCLUSIONS

Alfuzosin is an effective alpha-blocker in the treatment of MetS patients with moderate LUTS. Nevertheless, the effectiveness of alfuzosin therapy was found to be greater in non-MetS patients, which implicates that MetS might have an adverse effect on the BPH treatment, though in a limited fashion. Further placebo-controlled studies with larger patient populations are needed to substantiate our findings.

CONFLICTS OF INTEREST

All authors declare that, there is no conflicts of interest in connection with this paper.

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