

The relationship between heart failure and smoking, and development of urethral stricture

Relación entre insuficiencia cardíaca, tabaquismo y desarrollo de estenosis uretral

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Abstract

Objective: To evaluate the relationship between heart failure (HF), chronic obstructive pulmonary disease (COPD), and smoking with the development of urethral stricture (US) by examining the patients who underwent transurethral prostate resection procedure, with and without the development of US in their follow-ups. **Methods:** Among the patients who underwent transurethral resection of the prostate, 50 patients who developed US during their follow-ups formed group 1, while a total of 50 patients who did not develop US and were selected by lot formed group 2. The relationship between the patients' data on HF, COPD and smoking status and the development of US was investigated. **Results:** The mean number of cigarettes smoked was statistically significantly high in the group with stricture ($p = 0.007$). Furthermore, pulmonary function test parameters of patients such as forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC), and FEV1/FVC were found to be statistically significantly higher in Group 2 ($p < 0.001$, $p < 0.001$, and $p = 0.008$, respectively). In the logistic regression analysis, being a smoker was found to be the strongest predictor ($p = 0.032$). **Conclusions:** Our study concluded that smoking, HF, and COPD significantly increase the risk of developing stricture after transurethral resection of the prostate.

Keywords: Urethral stricture. Transurethral prostate resection. Smoking. Chronic obstructive pulmonary disease. Heart failure.

Resumen

Objetivo: Evaluar la relación de la insuficiencia cardíaca, la enfermedad pulmonar obstructiva crónica y el tabaquismo con el desarrollo de estenosis de uretra en pacientes sometidos a resección transuretral de próstata con y sin desarrollo de estenosis de uretra en su seguimiento. **Métodos:** Cincuenta pacientes que desarrollaron estenosis de uretra durante su seguimiento formaron el grupo 1, y 50 pacientes que no desarrollaron estenosis de uretra y fueron seleccionados por lote formaron el grupo 2. Se investigó la relación de los datos de los pacientes sobre insuficiencia cardíaca, enfermedad pulmonar obstructiva crónica y tabaquismo con el desarrollo de estenosis uretral. **Resultados:** La media de cigarrillos fumados fue significativamente más alta en el grupo con estenosis ($p = 0.007$). Además, se encontró que los parámetros de las pruebas de función pulmonar de los pacientes, como FEV1, FVC y FEV1/FVC, eran significativamente más altos en el grupo 2 ($p < 0.001$, $p < 0.001$ y $p = 0.008$, respectivamente). **Conclusiones:** El tabaquismo, la insuficiencia cardíaca y la enfermedad pulmonar obstructiva crónica aumentan significativamente el riesgo de desarrollar estenosis después de una resección transuretral de próstata.

Palabras clave: Estenosis uretral. Resección transuretral de próstata. Tabaquismo. Enfermedad pulmonar obstructiva crónica. Insuficiencia cardíaca.

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Introduction

The incidence of urethral stricture (US) is estimated to be 0.3%, and it is more common in men over 55 years of age^{1,2}. The development of iatrogenic US took the first place with a high rate of 45% as a result of the increase and widespread use of diagnostic and therapeutic endourological approaches to urological diseases in recent years³.

Transurethral prostate resection (TURP) is the most important of these endoscopic urethral approaches. TURP is the most well-known, common, and gold-standard surgical treatment of benign prostatic hyperplasia⁴. US is one of the most common late complications of TURP, and its incidence has been reported as 13% in the literature⁵. According to the results of the patient follow-ups in the studies, most of the patients who developed US after transurethral surgery were observed to make a visit within the first 6 months, and the localization of the stricture was generally reported as the bulbar urethra^{6,7}.

When we look at the pathogenesis of stricture, leakage of urine into the subepithelial area after damage to the urethral epithelium for any reason has prognostic importance. Urine leaking into the subepithelial area triggers fibrotic processes through corpus spongiosum sinusoids and dense connective tissue intermediates⁸.

Oxygen is required as a precursor in all stages of wound healing. Moreover, the hypoxic state is a factor that plays a role in the execution of all of these processes through the hypoxia-inducible factor-1 (HIF-1) signaling pathway⁹. Abnormal wound healing caused by excessive accumulation of extracellular matrix elements by fibroblasts and myofibroblasts in the wound area is called fibrosis. In tissues where fibrotic healing begins to be observed, the tissue becomes hypoxic as a result of decreased vascular density. Studies indicate that the development and progression of fibrosis are associated with hypoxia, that is, profibrotic genes activated by HIF-1 α ^{10,11}.

There should be a balance between the need for oxygen and its transmission to maintain physiological events in the body. The two main organ systems responsible for the delivery of oxygen to the body and maintaining homeostasis are the respiratory and the cardiovascular systems. Abnormal functions of either of these two would lead to the development of hypoxemia and its harmful consequences¹².

Heart failure (HF), chronic obstructive pulmonary disease (COPD), and smoking are comorbidities that cause ventilation/perfusion mismatch systemically. These conditions can cause hypoxemia in systemic arterial blood and microvascular areas. The negative effects of smoking on wound healing were first shown in a study conducted in 1977¹³. In a retrospective study in which 3500 cases were examined, COPD has been emphasized to be a potential risk factor for wound dehiscence¹⁴. Especially in the older adult patient population, HF is considered responsible for the development of complicated wounds¹⁵.

US which develops in patients who underwent TURP for bladder outlet obstruction is an important complication. We could not come across any study in the literature drawing attention to the relationship between this condition and HF, COPD, and smoking. However, studies show that smoking after surgeries such as radical prostatectomy and urethroplasty is a factor that leads up to the development of stricture^{16,17}. Similarly, COPD and cardiac pathologies were shown to increase the relapse rate of it after internal urethrotomy¹⁸.

Based on all this information, it was aimed to evaluate the relationship between HF, COPD, and smoking with the development of US by examining the patients who underwent TURP procedure, with and without the development of US in their follow-ups.

Materials and methods

Study population

This study was conducted in the urology and chest diseases department of Afyonkarahisar Health Sciences University Hospital between February 2021 and August 2021. The study data were collected retrospectively after obtaining the ethical approval (2011-KAEK-2 2021/2) for the study from the Clinical Research Ethics Committee of Afyonkarahisar Health Sciences University. It was conducted in accordance with the principles of the Declaration of Helsinki. The purpose and the study process were explained to the patients in detail, and then written informed consent was obtained from each patient.

Among the 834 patients who underwent TUR-P between 2017 and 2021, 102 patients did not attend their follow-up visits for at least 6 months after the operation. Seventy-eight patients were excluded from the study considering the stated exclusion criteria. During

the follow-up, 32 patients who underwent traumatic catheterization due to urinary retention or severe low urinary tract symptoms (LUTS), urethra dilatation, percutaneous cystostomy, complicated urethral stenosis, and prostatic urethra or meatus stenosis were excluded from the study. Among the remaining 622 patients, penile or bulbar urethral stenosis was detected in 63 patients as a result of diagnostic evaluations performed with cystoscopy during their follow-up. Our stenosis rate was found to be 10.1% in patients who had regular check-ups and had a known medical history. Among these patients, 50 patients were selected using the randomizer.org system. Among the remaining 559 patients, 50 patients were randomly selected as the control group, again using the randomizer.org system.

History of following conditions as pelvic radiotherapy, neurogenic bladder, bladder cancer, US before TURP, bladder stones, urethritis with a definitive diagnosis, lichen sclerosus, high-energy pelvic trauma/fracture and urethral anomaly (Hypospadias etc.), and malignancy in TURP pathology and diagnosis of prostate cancer were the exclusion criteria.

Application

Anamnesis, detailed physical examination, DRM, UFM, PVR and prostate volume measurement with transabdominal ultrasonography, serum PSA, TIT, urine culture, chest X-ray, electrocardiography, complete blood count, blood biochemistry analysis, coagulation tests, and viral marker tests were evaluated preoperatively for all patients who underwent transurethral resection of the prostate. Anaesthesia, cardiology, and pulmonology consultation reports in which patients were consulted for pre-operative evaluation purposes were noted.

Name-surname, age, height, weight, smoking status (packs/year), pre-operative UFM data, IPSS and QoL data for symptom severity, PVR, and prostate volumes (cm³) evaluated by transabdominal USG of the participants were recorded in the individual files of the patients. Furthermore, ACC/AHA stage, scores of mMRC scale, and COPD CAT were created in line with the verbal responses from the patient used to predict the level of comorbidities such as HF and COPD and information obtained from cardiology and chest diseases department consultation reports preoperatively. Pulmonary function testing (spirometry) and clinical evaluation results carried out by a pulmonologist were recorded.

All patients were selected from cases operated by three urologists, each with more than 100 TURP case experiences. In all operations, resection was routinely performed with an Olympus 26-Fr permanent current resectoscope and standard electrode (Olympus Winter and Ibe GmbH, Germany) under irrigation of saline (0.9% sodium chloride), and a bipolar plasma kinetic energy source was used. After the operation, a 22-Fr 3-way R sch brand catheter was inserted in all patients, and continuous bladder irrigation, started immediately with saline (0.9% sodium chloride) in a way that the urine color was clear, and was routinely continued until the morning of the 1st post-operative day. The catheters of the patients were removed between 3 to 6 days.

Patients' data on post-operative follow-up, infection status, storage symptoms, US status, UFM, PVR, and IPSS-QoL were recorded on their files. Internal urethrotomy was performed using a cold knife with a Storz 21-Fr Sacshe model optical urethrotome as a standard on patients who were found to have penile or bulbar US according to the diagnostic evaluations during their follow-ups. All patients evaluated in the stenosis group in the study had stenoses shorter than 2 cm and uncomplicated.

While 50 patients in whom penile or bulbar US was detected at least once in their follow-ups after the TURP operation formed Study Group 1, 50 patients selected by lot among the patients in whom no stricture was detected formed Study Group 2.

Statistical analysis

Statistical analysis of the study data was performed using the IBM Statistical Package for the Social Sciences version 15.0 program. The Kolmogorov–Smirnov test was used to check whether the variables had a normal distribution. In the comparison of paired groups, Student's t-test was used for normally distributed parameters and the Mann–Whitney U-test was used for the parameters which did not have normal distribution parameters. The Chi-square test or Fisher's Exact test was used for the evaluation of multi-well crosstabs. In multivariate analysis, independent predictors of stricture development were examined with the enter method and binary logistic regression analysis using possible factors identified in previous analyzes. The Hosmer–Lemeshow test was used for model fit. Results with a type 1 error level of $p < 0.05$ were considered statistically significant.

Results

The quantitative parameters of the patients such as age, body mass index (BMI), and number of cigarettes smoked (packs/year) evaluated before the operation was given as mean and standard deviation, and were compared for Group 1 and Group 2, and the results are presented in Table. No statistically significant difference was found between the ages of the patients in both groups ($p = 0.368$). While the mean BMI value of the patients in group 1 was $27.43 \pm 3.17 \text{ kg/m}^2$, it was $25.95 \pm 2.78 \text{ kg/m}^2$ in group 2, and the mean BMI value was found to be statistically significantly higher in the group with stricture. Similarly, while the mean number of cigarettes smoked in group 1 was 23.78 ± 18.2 packs/year, it was 13.94 ± 19.94 packs/year in group 2 and the mean number of cigarettes smoked was found to be statistically significantly higher in the group with stricture ($p = 0.007$) (Table 1).

Data that are considered to be predictors of LUTS such as prostate volume, Qmax, PVR, IPSS, and QoL evaluated preoperatively, and surgery-related variables such as duration of operation and duration post-operative catheter stay were given as mean and standard deviation and were compared for Group 1 and Group 2, and the results are presented in the Table. When the table is examined, there was no statistically significant difference between the two groups in terms of prostate volume, Qmax, IPSS, QoL, duration of operation, and post-operative catheter stay parameters ($p = 0.126$, $p = 0.059$, $p = 0.102$, $p = 0.555$, $p = 0.102$, and $p = 0.571$, respectively). The PVR value measured before the operation in group 1 was found to be significantly higher than in group 2 ($p = 0.007$) (Table 1).

The staging of patients in terms of HF was performed according to the ACC/AHA system, a classification based mainly on symptoms and exercise capacity. Eighteen patients with no abnormality in their cardiac structures and no risk factors for the development of HF were not included in this classification (Table 2). While Stage A and Stage B patients were asymptomatic patients in terms of HF, with 18 patients not included in this classification, HF symptoms were observed in Stage C and Stage D patients. Symptomatic and asymptomatic patient groups in terms of HF were examined in the crosstabs with Group 1 and Group 2. While the rate of symptomatic HF was 56% in Group 1, it was 26% in Group 2. The patients with symptomatic HF were determined to have a statistically significantly higher rate

Table 1. Comparison of pre-operative and intraoperative data between groups

Patient data	Group 1 (n = 50)	Group 2 (n = 50)	p-value
	Mean $\pm$ SD	Mean $\pm$ SD	
Age (years)	67.94 $\pm$ 8.07	66.62 $\pm$ 8.16	0.368
BMI (kg/m ²)	27.43 $\pm$ 3.17	25.95 $\pm$ 2.78	0.015
Number of cigarettes (packs/year)	23.78 $\pm$ 18.2	13.94 $\pm$ 19.94	0.007
Prostate volume (cm ³)	63.68 $\pm$ 23.78	56.42 $\pm$ 23.19	0.126
Qmax (ml/sec)	7.88 $\pm$ 3.22	6.72 $\pm$ 2.75	0.059
PVR(cm ³)	152.06 $\pm$ 83.51	112.78 $\pm$ 66.94	0.007
IPSS	20.4 $\pm$ 5.22	22.04 $\pm$ 4.7	0.102
QoL	3.5 $\pm$ 0.99	3.66 $\pm$ 0.87	0.555
Duration of operation (min)	49 $\pm$ 17.78	43 $\pm$ 17.14	0.102
Duration of catheter stay (days)	3.76 $\pm$ 0.79	3.66 $\pm$ 0.71	0.571

BMI: body mass index; Qmax: maximum urine flow rate; PVR: post-void residual; IPSS: international prostate symptom score; QoL: quality of life; Mean $\pm$ SD: mean $\pm$ standard deviation.

Table 2. ACC/AHA staging of patients

Number of Patients	None	Stage A	Stage B	Stage C	Stage D	Total
Number of Patients	18	26	15	32	9	100

Table 3. Distribution of two groups according to HF symptom status and Chi-square test

HF symptom status	Group 1 (n = 50)	Group 2 (n = 50)	Total	p-value
No symptoms	22	37	59	0.002
With symptoms	28	13	41	
Total	50	50	100	

HF: heart failure.

of stricture development, which was found with the Chi-square test ($p = 0.002$) (Table 3). The data obtained from the mMRC scale and CAT scores, which evaluate the pulmonary functions of the patients before the operation, and the pulmonary function testing parameters such as forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC), and FEV1/FVC

were given as mean and standard deviation and were compared for Group 1 and Group 2, and the results are presented in the Table. The mean mMRC scale and CAT scores of the patients in group 1 were found to be statistically significantly higher than those in group 2 ($p = 0.003$, $p = 0.002$, respectively). FEV1, FVC, and FEV1/FVC values, on the other hand, were found to be statistically significantly lower in Group 1 compared to Group 2 ($p < 0.001$, $p < 0.001$, $p = 0.008$, respectively) (Table 4).

When the PFT results were evaluated, 35 out of 100 patients were considered to have COPD due to the detection of FEV1/FVC $<70\%$ after bronchodilator. Groups of patients with and without COPD were examined in crosstabs with Group 1 and Group 2. While the rate of COPD was 48% in Group 1, it was 22% in Group 2. The patients with COPD were determined to have a statistically significantly higher rate of stricture development, which was found with the Chi-square test ($p = 0.006$) (Table 5).

When the group that developed stricture in the post-operative follow-up was examined, the mean time to develop stricture was found to be 7.04 ± 3.75 months. When the relationship between being a smoker, HF symptom status, and the status of having COPD and the duration of stricture development was evaluated, no statistically significant finding was found.

Binary logistic regression analysis was used to identify the possible independent predictors of stricture development that contributed the most to the outcome. Being a smoker, the number of cigarettes smoked, BMI value, pre-operative PVR, symptomatic HF, scores of mMRC scale and CAT, FEV1/FVC, and COPD status were used as predictors. The model predicting the development of stricture was significant ($\chi^2(8) = 4.26$, $p = 0.832$) and explained 32.7% of the variance (Nagelkerke $R^2 = 0.327$). The model correctly predicted 70% of non-relapsed and 72% of relapsed (71% overall). Smoking, the number of cigarettes smoked, and the pre-operative PVR value were important predictors for the development of stricture. Being a smoker was found to be the strongest predictor among these parameters in the model ($p = 0.032$). One unit increase in the number of cigarettes smoked increased the risk of stricture by 2 units (Table 6).

Discussion

The development of US after TURP has been reported in the literature in recent years, in the range of approximately 9.8-13%^{5,19}. Prevention of

Table 4. Comparison of data evaluating patients' respiratory functions

Respiratory function data	Group 1 (n = 50)	Group 2 (n = 50)	p-value
	Mean $\pm$ SD	Mean $\pm$ SD	
mMRC	1.07 $\pm$ 1.54	0.68 $\pm$ 1.25	0.003
CAT	14.6 $\pm$ 10.06	8.66 $\pm$ 7.98	0.002
FEV1 (%)	71.02 $\pm$ 22.69	87.36 $\pm$ 15.19	<0.001
FVC (%)	83.18 $\pm$ 16.31	95.84 $\pm$ 10.14	<0.001
FEV1/FVC (%)	66.6 $\pm$ 10.84	72.5 $\pm$ 6.69	0.008

mMRC: modified medical research council; CAT: COPD assessment test; FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; Mean $\pm$ SD: mean $\pm$ standard deviation.

Table 5. Distribution of two groups according to COPD status and Chi-square test

COPD status	Group 1 (n = 50)	Group 2 (n = 50)	Total	p-value
No COPD	26	39	65	0.006
With COPD	24	11	35	
Total	50	50	100	

COPD: chronic obstructive pulmonary disease.

Table 6. Predictors for the development of stricture

Risk factor	Development of stricture	
	RR (95% CI)	p-value
Smoking	7.39 (1.18-46.18)	0.032
Number of cigarettes	0.94 (0.88-0.99)	0.042
BMI	1.18 (0.99-1.39)	0.052
PVR	1.00(1.00-1.01)	0.042
Symptomatic HF	4.66 (0.39-54.58)	0.220
mMRC	0.79 (0.29-2.10)	0.638
CAT	1.06 (0.93-1.21)	0.335
FEV1/FVC	0.95 (0.85-1.06)	0.377
COPD	1.11 (0.15-7.97)	0.918

BMI: body mass index; PVR: post-void residual; HF: heart failure; mMRC: modified medical research council; CAT: COPD assessment test; FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; COPD: chronic obstructive pulmonary disease.

stricture development after diagnostic or therapeutic endourological procedures or reduction of high relapse rates after transurethral treatments such as internal urethrotomy carried out on advanced US is the main

goal of the US approach, considering the high treatment costs²⁰.

Both adequate oxygenation of tissue and hypoxia are necessary factors for normal wound healing²¹. The hypoxic environment at the beginning of wound healing plays an early stimulating role in tissue repair and angiogenesis through HIF-1^{9,21}. However, the finding that the proliferative rate of fibroblasts increases by 71% if the hypoxic environment lasts for more than 72 h is thought-provoking for fibrotic pathologies²². Recent studies have shown that profibrotic genes associated with HIF-1 α , that is, hypoxia-induced, are effective in the development of fibrosis²³. More studies are being conducted on HIF-1 α inhibition for the treatment and prevention of fibrotic diseases²⁴.

Hypoxia and hypoxemia describe different conditions. Hypoxemia refers to a decrease in partial oxygen pressure in the blood, while hypoxia refers to decreased tissue oxygenation. Hypoxemia might lead to hypoxia as a result. The most common cause of hypoxemia is ventilation/perfusion mismatch and it benefits from complementary oxygen therapies^{12,25}.

Based on these considerations, in our study, we aimed to evaluate the relationship between HF, COPD, and smoking with the development of US by making a comparison between the patients with US development in their follow-ups after the TURP operation and those without. HF, COPD, and smoking are comorbidities that cause ventilation/perfusion mismatch systemically. These conditions can cause hypoxemia in systemic arterial blood and microvascular areas and thus hypoxia at the tissue level.

There are studies on medical treatment options that can prevent the development of US in the literature. However, there is no method that was accepted and included in the treatment routine yet.

In their study in 2014, Ateş et al. evaluated the effectiveness of hyperbaric oxygen therapy (HBOT) on hypospadias cases that they treated with the help of a buccal mucosal graft. The success rate was found to be significantly higher in the patient groups who were given HBOT after both the first surgery and the second surgery stages. They reported in their conclusion that HBOT can be used as an alternative method to increase the success of the procedure in these patients²⁶.

In an experimental study conducted in Ankara, Türkiye, the early administration of dexamethasone to rats with urethral damage has been shown to significantly reduce inflammation and spongioblastosis and it was suggested that it would be beneficial in preventing the development of US after urethral damage²⁷.

A US-based study suggested that the mechanism responsible for the development of US was urethral fibrosis resulting from altered or increased fibroblast activity within the tissue. In this study, the application of an antifibrotic agent mitomycin C in addition to internal urethrotomy was compared and it was resented as an alternative option for poor open surgery candidates and patients who require repeated multiple internal urethrotomy²⁸.

In the study conducted by Dalkılıç et al. in 2018, the effect of low molecular weight heparin (LMWH), which is mainly used as an anticoagulant, on the incidence of US in patients who underwent TURP operation was investigated since it was presented to have antifibrotic effects. Given the relapse and urethroplasty rates, the incidence of developing severe US was concluded to be less in those receiving anticoagulant therapy with LMWH²⁹.

In the literature review conducted, we did not come across any study that found a direct relationship between the development of US after TURP and smoking. In their study in which a total of 467 patients who underwent radical prostatectomy have been reviewed retrospectively, Borboroglu et al. indicated that smoking significantly increased the risk of vesico US development¹⁷.

There are studies with different opinions about smoking among studies evaluating which factors could be associated with stricture relapse after urethroplasty. Some studies suggest that smoking increases the rate of stricture relapse after urethroplasty¹⁶. One of the important studies is the study by Whitson et al. in 2008. They, in their study, concluded that smoking was a predictor of failure in patients who underwent fasciocutaneous flap urethroplasty³⁰. On the other hand, many studies, especially Kinnaird et al.'s study in which they evaluated 604 urethroplasty cases retrospectively, state that smoking is not associated with relapse³¹.

There is also a similar difference of opinion on the relationship between relapse after internal urethrotomy and smoking. Aydemir et al., as a result of the retrospective analysis of the data of 94 patients, suggested that smoking increases relapse after internal urethrotomy³². On the contrary, Redon-Galvez et al. argued in a similar study that age, weight, smoking status, and cardiovascular risk factors did not have a significant effect on relapse after internal urethrotomy³³.

The mean number of cigarettes smoked in the group with stricture was statistically significantly higher than the control group in our study ($p = 0.007$). In the logistic regression analysis carried out to identify the possible

independent predictors of stricture development that contributed the most to the outcome, smoking was found to be the strongest predictor in the model ($p = 0.032$). One unit increase in the number of cigarettes smoked increased the risk of stricture by 2 units. The number of cigarettes smoked was also found to be high in patients with stricture who had a relapse after internal urethrotomy, but this difference was not statistically significant ($p = 0.732$).

Sinanoglu et al. suggested in their retrospective review of TURP data of 317 patients with different comorbidities that COPD was not a risk factor for the development of post-operative stricture³⁴. In another study with a similar design, the minimum triple combinations of diabetes mellitus (DM), hypertension, coronary artery disease (CAD), and COPD comorbidities were determined to pose a risk in the development of stricture after internal urethrotomy¹⁸. The erectile dysfunction status of 41 patients with COPD was investigated in another study in which the severity of erectile dysfunction was observed to increase as the pulmonary function test parameters FEV1, FVC, and FEV1/FVC levels decreased³⁵. Given that the penis and urethra are both supplied with blood by the internal pudendal artery, it was thought that there may be a connection between erectile perfusion and urethral ischemia.

In our study, COPD, as an independent comorbidity, was found in a higher number of patients in the group with stricture, which was statistically significant ($p = 0.006$). The mMRC scale and CAT test results evaluating the patients in terms of respiratory symptoms and severity of dyspnea were significantly higher in the stricture group ($p = 0.003$, $p = 0.002$, respectively). Levels of the pulmonary function test parameters FEV1, FVC, and FEV1/FVC levels were significantly lower in the stricture group ($p < 0.001$, $p < 0.001$, $p = 0.008$, respectively).

Sinanoglu et al. concluded in their study that comorbidities such as HT, DM, and CAD (Congenital Adrenal Hyperplasia) are risk factors for the development of US, especially in patients who underwent plasma kinetic TURP³⁴. There are also studies showing that the same comorbidities are associated with the development of stricture after radical prostatectomy^{17,18,32} and relapse after internal urethrotomy. In a study conducted by Ruutu et al., among the patients who underwent open heart surgery and had a short-term urethral catheter and did not develop mortality in their 1-year follow-ups, 16.6% of them were found to have US developed³⁶. In another study, the severity of CAD has been found to be associated with the US development in patients who

underwent cardiac angiography for acute coronary syndrome and had a urethral catheter placed³⁷.

In our study, patients were evaluated for HF using the ACC/AHA classification. After that, they were grouped as asymptomatic and symptomatic patients in terms of HF. The reason for this is that the hypoxemia picture, considered responsible for the pathogenesis in our study, was encountered only in symptomatic HF patients. When evaluated in this way, it was observed that there were many symptomatic HF patients at a statistically significant level in the group that developed stricture ($p = 0.002$).

In the literature, US has been observed to be detected in the first 6 months on average after TURP⁶. This period was 7.04 months in our study on average and was similar to the literature. There was no significant relationship between HF, COPD, smoking, and duration of stricture development.

Our study has some limitations. These include; the retrospective design of the study and the inability to perform histological examination because urethral tissue was not taken. In addition, smoking, COPD, and HF were evaluated using scales. Comorbidity studies detailed with physiometric and radiological imaging may contribute to the literature.

Conclusion

In our study, we concluded that smoking, HF, and COPD significantly increase the risk of stricture development after TURP. The symptom scores and each of the pulmonary function test parameters used in the diagnosis of COPD were determined to have a statistically significant relationship with stricture development. Among the possible independent predictors for stricture development, smoking was found to be the strongest predictor in the model.

Given these conclusions, it is believed that the hypoxemic picture should be closely monitored in the pre-operative, intraoperative, and post-operative periods in patients who would undergo TURP operation and remedial treatments and measures should be taken to reduce the rate of US development. Furthermore, patients who are planned for TURP and who are at high risk of developing US considering these factors can be provided more detailed information about the complications that might develop before the procedure, and they could be informed that they have a higher risk for this condition. Thus, despite the complications that might occur in the post-operative

period, higher patient satisfaction and a conscious patient profile can be achieved.

The implications of our study need to be supported by more randomized controlled studies and meta-analyses as required by evidence-based science.

Authors' contributions

K.T, A.D, O.G., and I.K. designed the study; K.T, K.U, A.B, and M.K. recruited the participants and collected the data; K.T, O.G., and I.K. performed the statistical analysis; K.T, A.D, and A.B interpreted the data; K.T. drafted the first manuscript; and all authors critically reviewed the paper.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study. This study was approved by the Local Ethics Committee (AFSU 2011-KAEK-2/2021/2) and was conducted in accordance with the ethical standards of the Declaration of Helsinki.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

References

1. Santucci RA, Joyce GF, Wise M. Male urethral stricture disease. *J Urol*. 2007;177:1667-74.
2. McMillan A, Pakianathan M, Mao J, Macintyre C. Urethral stricture and urethritis in men in Scotland. *Sexually Transmitted Infections*. 1994;70:403-5.
3. Tritschler S, Roosen A, Füllhase C, Stief CG, Rübber H. Urethral stricture: etiology, investigation and treatments. *Dtsch Arztebl Int*. 2013;110:220.

4. AUA Practice Guidelines Committee. AUA guideline on management of benign prostatic hyperplasia (2003). Chapter 1: diagnosis and treatment recommendations. *J Urol*. 2003;170:530-47.
5. Cornu JN, Ahyai S, Bachmann A, de la Rosette J, Gilling P, Gratzke C, et al. A systematic review and meta-analysis of functional outcomes and complications following transurethral procedures for lower urinary tract symptoms resulting from benign prostatic obstruction: an update. *Eur Urol*. 2015;67:1066-96.
6. Chung JH, Kang DH, Moon HS, Jeong TY, Ha US, Han JH, et al. Effects of hyaluronic acid and carboxymethylcellulose on urethral stricture after transurethral resections of the prostate for benign prostatic hyperplasia: a multicenter, single blinded, randomized controlled study. *J Endourol*. 2013;27:463-9.
7. Mundy A. The treatment of sphincter strictures. *Br J Urol*. 1989;64:626-8.
8. Hakky S. Ultrastructure of the normal human urethra. *Br J Urol*. 1979;51:304-7.
9. Semenza GL, Wang GL. A nuclear factor induced by hypoxia via de novo protein synthesis binds to the human erythropoietin gene enhancer at a site required for transcriptional activation. *Mol Cell Biol*. 1992;12:5447-54.
10. Zeisberg M, Kalluri R. Cellular mechanisms of tissue fibrosis. 1. Common and organ-specific mechanisms associated with tissue fibrosis. *Am J Physiol Cell Physiol*. 2013;304:C216-25.
11. Kaminski N, Rosas IO. Gene expression profiling as a window into idiopathic pulmonary fibrosis pathogenesis: can we identify the right target genes? *Proc Am Thorac Soc*. 2006;3:339-44.
12. Sarkar M, Niranjana N, Banyal PK. Mechanisms of hypoxemia. *Lung India*. 2017;34:47-60.
13. Mosely LH, Finseth F. Cigarette smoking: impairment of digital blood flow and wound healing in the hand. *Hand*. 1977;9:97-101.
14. Spiliotis J, Tsiveriotis K, Datsis AD, Vaxevanidou A, Zacharis G, Gafis K, et al. Wound dehiscence: is still a problem in the 21st century: a retrospective study. *World J Emerg Surg*. 2009;4:12.
15. Gould LJ, Fulton AT. Wound healing in older adults. *R I Med J* (2013). 2016;99:34.
16. Breyer BN, McAninch JW, Whitson JM, Eisenberg ML, Mehdizadeh JF, Myers JB, et al. Multivariate analysis of risk factors for long-term urethroplasty outcome. *J Urol*. 2010;183:613-7.
17. Borboroglu PG, Sands JP, Roberts JL, Amling CL. Risk factors for vesicourethral anastomotic stricture after radical prostatectomy. *Urology*. 2000;56:96-100.
18. Kurtulus FO, Akgün FS. Long-term effect of colchicine treatment in preventing urethral stricture recurrence after internal urethrotomy. *Urol J*. 2018;15:204-8.
19. Rassweiler J, Teber D, Kuntz R, Hofmann R. Complications of transurethral resection of the prostate (TURP)-incidence, management, and prevention. *Eur Urol*. 2006;50:969-80.
20. Greenwell T, Castle C, Andrich D, MacDonald J, Nicol D, Mundy A. Repeat urethrotomy and dilation for the treatment of urethral stricture are neither clinically effective nor cost-effective. *J Urol*. 2004;172:275-7.
21. Tandara AA, Mustoe TA. Oxygen in wound healing-more than a nutrient. *World J Surg*. 2004;28:294-300.
22. Siddiqui A, Galiano RD, Connors D, Gruskin E, Wu L, Mustoe TA. Differential effects of oxygen on human dermal fibroblasts: acute versus chronic hypoxia. *Wound Repair Regen*. 1996;4:211-8.
23. Tzouveleki A, Harokopos V, Paparountas T, Oikonomou N, Chatziioannou A, Vilaras G, et al. Comparative expression profiling in pulmonary fibrosis suggests a role of hypoxia-inducible factor-1α in disease pathogenesis. *Am J Respir Crit Care Med*. 2007;176:1108-19.
24. Ruthenberg RJ, Ban JJ, Wazir A, Takeda N, Kim JW. Regulation of wound healing and fibrosis by hypoxia and hypoxia-inducible factor-1. *Mol Cells*. 2014;37:637-43.
25. Belda F, Soro M, Ferrando C. Pathophysiology of respiratory failure. *Trends Anaesth Crit Care*. 2013;3:265-9.
26. Ateş F, Aktas Z, Okcelik S, Dursun F, Memis A, Mutluoglu M, et al. The role of hyperbaric oxygen therapy in adult hypospadias surgery with buccal mucosal tube urethroplasty. *Eur Urol*. 2014;13:e1617.
27. Yardimci I, Karacan T, Resorlu B, Doluoglu OG, Ozcan S, Aydin A, et al. The effect of intraurethral dexamethasone on healing and fibrosis in rats with experimentally induced urethral trauma. *Urology*. 2015;85:274. e9-13.
28. Farrell MR, Lawrenz CW, Levine LA. Internal urethrotomy with intralesional mitomycin C: an effective option for endoscopic management of recurrent bulbar and bulbomembranous urethral strictures. *Urology*. 2017;110:223-7.
29. Dalkilic A, Yavuzsan A, Yesildal C, Şimşek A, Aydin A, Bayar G, et al. Retrospective analysis of urethral stenosis following transurethral prostate resection: preventing effect of the using low molecular weight heparin on development of urethral stenosis. *J Reconstr Urol*. 2018;8:85-90.
30. Whitson JM, McAninch JW, Elliott SP, Alsikafi NF. Long-term efficacy of distal penile circular fasciocutaneous flaps for single stage reconstruction of complex anterior urethral stricture disease. *J Urol*. 2008;179:2259-64.
31. Kinnaird AS, Levine MA, Ambati D, Zorn JD, Rourke KF. Stricture length and etiology as preoperative independent predictors of recurrence after urethroplasty: a multivariate analysis of 604 urethroplasties. *Can Urol Assoc J*. 2014;8:E296.

32. Aydemir H, Sağlam HS, Köse O, Erdik A, Halis F, Gökçe A. The effect of recurrent direct vision internal urethrotomy for short anterior urethral strictures on the disease course and the predictors of treatment failure. *Can Urol Assoc J.* 2019;13:E366.
33. Redon-Galvez L, Molina-Escudero R, Álvarez-Ardura M, Otaola-Arca H, Parra RA, Pérez-Borda Á. Predictors of urethral stricture recurrence after endoscopic urethrotomy. *Actas Urol Esp.* 2016;40:529-33.
34. Sinanoglu O, Ekici S, Balci MC, Hazar AI, Nuhoglu B. Comparison of plasmakinetic transurethral resection of the prostate with monopolar transurethral resection of the prostate in terms of urethral stricture rates in patients with comorbidities. *Prostate Int.* 2014;2:121-6.
35. Dunder M, Karadag F, Kocak I, Çıldag O. Kronik obstrüktif akciğer hastalığında erektil disfonksiyon ve hipoksemi ile ilişkisi. *Türk Ürol Derg.* 2001;27:84-9.
36. Ruutu M, Alfthan O, Heikkinen L, Järvinen A, Kontinen M, Lehtonen T, et al. Unexpected urethral strictures after short-term catheterization in open-heart surgery. *Scand J Urol Nephrol.* 1984;18:9-12.
37. Yildiz I, Gokalp F, Burak C, Karazindiyanoğlu S, Yıldız PO, Rencuzogullari I, et al. Relationship between the severity of coronary artery disease and catheter-associated urethral stricture in patients with acute coronary syndrome. *J Tehran Univ Heart Center.* 2020; 15:113.