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Original Scientific Paper

ETIOLOGY OF URETHRAL STRICTURE: A TERTIARY CENTER'S EXPERIENCE

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SUMMARY — Urethral stricture is a complex disease with an etiology that remains insufficiently studied. The frequency of etiological factors associated with urethral stricture has undergone significant changes in recent decades, considering geographical factors, socioeconomic characteristics of the population, and the different etiological factors present in developed and developing countries. We retrospectively collected data from 146 patients who underwent urethroplasty for urethral stricture between 2009 and 2019 at the University Clinical Center of Serbia (Belgrade, Serbia). The patients with urethral stricture were divided into several groups based on their age and the localization of the stricture. Eleven causes of urethral stricture were identified. Urethral catheterization was the leading cause of strictures, regardless of age, accounting for 48.6% of all patients ($p<0.001$). The most common localization was the penile urethra, accounting for 41.8% of patients ($p<0.001$), whereas posterior strictures were observed in only 5 patients (3.4%). Considering etiology, iatrogenic (catheterization) and idiopathic urethral stenosis are the predominant factors. Careful urethral manipulation during catheterization is crucial, as it contributes to the prevention of the most common etiological factor of urethral stricture.

Keywords: *Catheterization*; *Epidemiology*; *Etiology*; *Stricture*; *Urethra*; *Urethroplasty*

Introduction

Urethral stricture is a complex disease with an etiology and epidemiological characteristics that remain insufficiently studied. In addition to negatively affecting the quality of life, this disease has a significant socioeconomic component and strains healthcare systems[1,2]. As treatment often requires repeated procedures, healthcare systems are primarily strained by the significant funding required to treat patients with this disease[3]. Considering the structural complexity of the male urethra, there are different causes and stricture characteristics of its different sections[4]. Research on this topic indicates a significant shift in the frequency of urethral stricture etiological factors over the past few decades. In the past, infections such as gonococcal urethritis largely caused this disease, whereas other etiological factors, such as iatrogenic causes and traffic trauma, have become more prominent over time.

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For instance, performing endoscopic procedures in urology has led to iatrogenic injuries to the urethra, which are regarded as etiological factors of diseases that did not exist earlier[5]. Furthermore, differences in the causes of urethral strictures have been observed. Considering the geographical factors and socioeconomic characteristics of the population led to the identification of different etiological factors in developed and developing countries[3,5].

To date, only a few studies have examined the etiology of urethral strictures, and no study has been published that specifically addresses the etiology of urethral strictures in Serbia and the region of Southeast Europe, which is highly specific considering its geographical and socioeconomic characteristics. Adult patients from Serbia and its surrounding countries are treated at the Clinic of Urology at the University Clinical Center of Serbia, a tertiary healthcare institution.

This study aimed to evaluate urethral strictures comprehensively. It primarily focused on evaluating stricture etiology, including its accompanying characteristics (localization and stricture length), as well as the general characteristics of patients treated at a tertiary healthcare institution, to obtain concrete data on the etiology, possible prevention of strictures, and treatment strategy.

Materials and Methods

This study was conducted by retrospectively collecting data from patients who underwent surgical treatment for urethral stricture at the Clinic of Urology, University Clinical Center of Serbia, Belgrade. The study included data from patients who underwent urethroplasty between 2009 and 2019. Data on age, localization, and stricture length were obtained from the patients' medical history. The diagnosis of urethral stricture is established based on contrast imaging (retrograde urethrocystography and anterograde cystourethrography) and urethroscopy. Stricture length was measured intraoperatively.

This study was approved by the Ethics Committee of the University Clinical Center of Serbia (number 350/2019). To observe the localization of urethral stricture, we followed the anatomical division of the urethra into the penile, bulbous, and posterior urethra. Urethral strictures that were present continuously in both the penile and bulbous urethra were classified as panurethral strictures.

Etiological factors were identified mostly in accordance with the recommendations of the *International Consultation of Urological Diseases*[6] (ICUD), a joint initiative of the World Health Organization (WHO) and the Société Internationale d'Urologie (SIU). Cases in which the cause of the stricture could not be identified were considered idiopathic. Iatrogenic causes of urethral strictures were classified according to the procedures that caused the strictures, whereas catheterization as an etiological factor was identified only in cases where no other urethral manipulation was applied. Traumatic causes of strictures were classified according to the mechanism of injury.

Patients were classified into two groups according to age: those younger than 45 years and those older than 45 years. We decided upon this classification by analyzing previous research on the etiology of urethral stricture while keeping in mind that in patients older than 45 years, there is a wider presence or different iatrogenic influences.

For statistical data processing, we employed both descriptive and analytical statistical methods. The difference in occurrence between patient subgroups was analyzed using Fisher's exact test. A p-value of <0.05 was considered statistically significant. For data processing, we used SPSS version 20 (Windows).

Results

Between 2009 and 2019, a total of 146 men underwent urethroplasty at the Clinic of Urology of the University Clinical Center of Serbia. The average age of the patients was 54.0 years (range 18-81 years). Of the total number, 39 patients were younger than 45 years, and 107 patients were 45 years or older.

The average length of the stricture was 5.2 cm. Considering the localization of the stricture, the most common was the penile urethral stricture, present in 61 patients (41.8%), which was significantly more common than strictures in other localizations ($p<0.001$). Bulbous urethral stricture was present in 42 patients (28.8%). Panurethral stricture was present in 38 (26.0%) patients. Posterior strictures were observed in 5 patients (3.4%).

We identified 11 causes of urethral strictures: infection, lichen sclerosus (LS), penile injuries, perineal injuries, pelvic injuries, urethral foreign body injuries, urethral catheterization, transurethral resection (TUR), prostatectomy (radical and simple), circumcision, and idiopathic. Iatrogenic causes were present in 84 (57.5%) patients, where urethral catheterization was the main cause, leading to strictures in 48.6% of all patients, which was by far more common than all other causes (p<0.001). After urethral catheterization, the most common cause was idiopathic (17.1%), followed by lichen sclerosus (11.6%) (Table 1).

Within the group of patients younger than 45 years, in 15 patients (38.5%), the cause of stricture was urethral catheterization, which was more common than other causes (p<0.001). Other causes are idiopathic (20.5%), infection (15.4%), and penile injuries (10.3%). Infections and penile injuries were significantly more common within this group of patients than in the group of patients aged 45 or older (p<0.001 and 0.005, respectively) (Table 1).

Within the group of patients aged 45 or older, urethral catheterization was also the most common cause of stricture compared with other etiological factors (p<0.001), and it was the cause in 56 (52.3%) patients. The second most common cause of stricture within this group was idiopathic (15.9%), followed by lichen sclerosus (14.0%) (Table 1).

In terms of localization, catheterization was the leading cause of penile strictures (50.8%), bulbous urethra (47.6%), and panurethral strictures (52.6%). The second most common cause of penile urethral stricture was lichen sclerosus, present in 23% of patients, followed by idiopathic causes (8.2%). Lichen sclerosus was a significantly more common cause of penile urethral stricture than other localizations (p=0.013). In bulbous urethra, after those caused by catheterization, strictures have most frequently been idiopathic (28.6%), followed by those caused by perineal injury (9.5%). Idiopathic strictures were more frequent in the bulbous urethra than in other localizations (p=0.02). Idiopathic strictures were the second most common among panurethral strictures (18.4%), followed by infection and lichen sclerosus (both 7.9%). The most common cause of posterior urethral stricture was pelvic fracture (40%) (Table 2).

Discussion

The etiological factors of urethral stricture have undergone significant changes over the past few decades. Based on the results of 20 research papers published between 1961 and 1981 on the etiology of urethral stricture, the leading cause of this disorder was post-infective sequelae, accounting for up to 40%

Table 1. Etiological factors of urethral strictures according to patient age

Etiology	No (%)	No (%)		p-value
		Younger than 45	45 or older	
Idiopathic	25 (17.1)	8 (20.5)	17 (15.9)	0.620
Infection	6 (4.1)	6 (15.4)	0	**<0.001**
Lichen sclerosus	17 (11.6)	2 (5.1)	15 (14.0)	0.241
Penile injuries	4 (2.7)	4 (10.3)	0	**0.005**
Perineal injuries	6 (4.1)	1 (2.6)	5 (4.7)	1.00
Pelvic injuries	3 (2.1)	1 (2.6)	2 (1.9)	1.00
Urethral foreign body	1 (0.7)	1 (2.6)	0	0.267
Catheterization	71 (48.6)	15 (38.5)	56 (52.3)	0.190
Transurethral resection	6 (4.1)	0	6 (5.6)	0.193
Prostatectomy	5 (3.4)	0	5 (4.7)	0.325
Circumcision	2 (1.4)	1 (2.6)	1 (0.9)	0.464
Total	146	39	107	

Table 2. Etiological factors of urethral strictures according to stricture localization

	Penile	**Bulbous**	**Panurethral**	**Posterior**
Etiology	No (%)	No (%)	No (%)	No (%)
Idiopathic	5 (8.2)	12 (28.6)	7 (18.4)	1 (20.0)
Infection	1 (1.6)	2 (4.8)	3 (7.9)	0
Lichen sclerosus	14 (23.0)	0	3 (7.9)	0
Penile injuries	4 (6.6)	0	0	0
Perineal injuries	1 (1.6)	4 (9.5)	1 (2.6)	0
Pelvic injuries	0	0	1 (2.6)	2 (40.0)
Urethral foreign body	1 (1.6)	0	0	0
Catheterization	31 (50.8)	20 (47.6%)	20 (52.6)	0
Transurethral resection	1 (1.6)	2 (4.8)	2 (5.3)	1 (20.0)
Prostatectomy	1 (1.6)	2 (4.8)	1 (2.6)	1 (20.0)
Circumcision	2 (3.3)	0	0	0
Total	61 (41.8)	42 (28.8)	38 (26.0)	5 (3.4)

of cases[7]. With the improvement of healthcare and the prevention of sexually transmitted diseases and their timely antibiotic treatment, a decrease in post-infective urethral strictures was observed between 1976 and 1981, together with an increase in idiopathic and iatrogenic causes[7]. Analyzing recent studies in developed countries has led to the conclusion that there is a rare occurrence of post-infective urethral strictures, which occurs in only 3% (0.4-3.7%) of all cases[4,5,8]. However, in developing countries, infections remain a significant cause of urethral stricture, occurring in up to 63% of cases[9]. On the other hand, there are differences between developing countries in terms of the presence of post-infective urethral strictures. According to data from a study in Brazil, a country with a rapidly growing economy, the occurrence of post-infective urethral stricture is only 4.6%, which is similar to that in developed countries[10]. In our study, the occurrence of infection as the cause of urethral stricture was also low (4.1%), which is similar to the situation in developed countries[4,5,8], and was significantly more frequent in patients younger than 45 years.

Lichen sclerosus was the cause of urethral stricture in 11.6% of our patients. After catheterization, LS was the second most common cause of penile urethral stricture (23.0%), which is in accordance with the results of other researchers, who identified it as one of the leading causes of penile urethral stricture (16-24%)[4,5,11], present in even up to 47% of stricture causes in fossa navicularis[12]. LS initially occurs in the preputium, glans, and meatus, and with the spread of the inflammatory process, it can lead to the proximal development of long and more complex urethral strictures[13,14]. The results of our research confirm this pathophysiological mechanism, as we, similarly to other researchers[4,5], also have not observed isolated bulbous urethral strictures caused by LS.

Palminteri *et al.* (2013) emphasized LS as the leading cause of panurethral strictures, stating that the strictures caused by LS are significantly longer than those of other etiology[4], which is in accordance with the development mechanism of these strictures. Similarly to other researchers, we did not observe posterior urethral stricture caused by LS, which confirms the assumption that LS does not occur in a different epithelium of this tract[4,5].

Iatrogenic strictures comprise up to 80% (32-79%) of all urethral strictures[8,15,16] in developed countries. In our patients, iatrogenic stricture was the leading cause in 57.5% of cases. In our research, the most common cause of iatrogenic urethral stricture, as well as the leading cause of all strictures in total, was urethral catheterization (48.6%), which is in accordance with previous studies that have proven that urethral catheterization

is among the leading causes of iatrogenic urethral stricture[4,5,10]. Traumatic or prolonged catheterization frequently causes panurethral and multifocal urethral strictures[4,5]. According to our research data, catheterization was the most common cause of panurethral strictures, accounting for 52.6% of cases. Kashefi *et al.* have shown that the incidence of urethral injury due to inappropriate catheterization was 3.2 urethral injuries per 1000 patients, but they have also emphasized the importance of the fact that inappropriate catheterization as a cause of urethral stricture could be prevented[17]. Research studies so far have indicated urethral ischemia as the possible pathophysiological mechanism for the occurrence of stenosing spongiofibrosis in patients with a catheter, especially in patients who are in hypovolemic conditions, such as patients with burns, polytraumas, and those who undergo open heart surgeries[8,18-20]. In addition, it should be noted that it was not possible to clearly separate whether other urological procedures followed by postoperative catheterization (such as transurethral resection, prostatectomy, or hypospadias surgery) could be the main cause of strictures, compared to urethral catheterization alone. Considering the high incidence of urethral strictures caused by catheterization, which are frequently panurethral and therefore complicated for treatment, the prevention of their occurrence is highly significant. Prevention of these strictures could be achieved by following strict indications for urinary catheterization, proper placement of the urinary catheter performed by trained medical staff, and placement of a suprapubic catheter when longer urine derivation is needed.

As previously stated, iatrogenic urethral strictures can occur after urological surgeries, such as TUR (2.2-9.8%), radical prostatectomy (8.4%), and simple prostatectomy (1.9%)[21-23]. These procedures are among the primary causes of urethral strictures in older patients[4,5]. In our study, TUR and prostatectomy were identified as causes of urethral strictures in only those patients aged 45 or older, causing within this group 5.6% and 4.7% of urethral strictures, respectively. Lumen *et al.* reported that TUR was the second most common cause of bulbous urethral stricture[5]. This result indicates possible urethral trauma in the area of the penoscrotal angle during resectoscope insertion[21].

Circumcision is one of the less common iatrogenic causes of urethral strictures. Meatal stenosis is a complication that can occur after circumcision. This complication often remains unrecognized in children after circumcision because longer follow-up appointments after surgery are usually not necessary. Possible mechanisms for the occurrence of meatal stenosis after circumcision are nonspecific inflammation and ischemia due to injury to the frenular artery[24].

By observing our patients, we found that none of the patients had a urethral stricture caused by hypospadias surgery. This finding is inconsistent with data from other studies, which indicate a significantly higher presence of this cause, especially in younger patients. Some studies even indicate that hypospadias surgery is the leading cause of penile urethral stricture (29-32%)[4,5,10]. This difference could partly be justified by the fact that other studies focused on a younger population (our youngest patient was 18 years old). Furthermore, the Clinic of Urology at the University Clinical Center of Serbia primarily treats adult patients, while surgeries for hypospadias in the pediatric population and the treatment of possible complications of these surgeries are performed at the Mother and Child Health Institute of Serbia and the Children's University Hospital.

In many cases, the cause is unknown; therefore, these strictures are considered idiopathic. In developed countries, idiopathic and iatrogenic strictures are the most common[4,5,8,25], and according to certain studies, idiopathic etiology is the leading cause (30-34%)[4,8]. In developing countries, considering the predominantly infective etiology, the presence of idiopathic strictures is lower than that in developed countries[2,9]. In 17.1% of our patients, the cause of urethral stricture could not be identified, making idiopathic strictures the second most common cause of stricture. After catheterization, these strictures were the second most frequent cause of stricture in the bulbous urethra in our patients. Lumen *et al.* have shown that the cause of bulbous urethral stricture cannot be identified in 48% of cases[5]. Considering the unknown mechanism of occurrence, several presumed causes of these strictures have been identified. It is believed that idiopathic strictures could be of congenital origin and could also be a delayed manifestation of unknown childhood trauma or even the effect of ischemia[26].

Trauma is a significant cause of urethral strictures, especially in developing countries, where traffic trauma

is more prevalent (21-31%)[10,27]. In our patients, trauma was the cause of urethral stricture in less than 10% (9.6%) of cases. Trauma was identified as the main cause of urethral stricture in younger patients, regardless of the injury mechanism[10]. Pelvic fractures, which are often a consequence of traffic traumatism, can occur together with urethral lesions at the bulbous-membranous junction (3-25%), with the consequential development of posterior urethral stricture[28,29]. Research results so far indicate pelvic fracture as the leading cause of posterior urethral stricture[4,5]. Perineal injuries, including straddle injuries, usually occur on the bulbous urethra, causing short stricture[5,6,8]. Penile injury, such as penile fracture or penetrating injury, could be the cause of anterior urethral stricture[30]. In our study, penile injury occurred more frequently in younger patients, causing 10.3% of strictures within this group. Among the traumatic causes, we observed a foreign body urethral injury in one of our patients, who developed a stricture after a urethral injury due to wire insertion. We have not encountered a similar example in other studies, which led to isolating this event as a special cause.

Conclusions

Our results indicate that the penile urethra is the most common stricture localization. Considering etiology, iatrogenic (primarily catheterization) and idiopathic urethral strictures take a leading position, regardless of patient age, while the difference indicated in the cases of etiological factors, such as infections and penile injuries, was significantly more common in younger patients than in the older population (aged 45 or more).

These findings indicate that adequate estimation and careful urethral manipulation during catheterization are necessary, as they contribute to the prevention of the most common etiological factor of urethral stricture.

Our research focused on patients treated with urethroplasty because we aimed to identify the causes of strictures that required complex treatment, which is possible only in a tertiary institution. The authors are aware that a large number of patients with urethral strictures are treated endoscopically or on an outpatient basis, which, on the one hand, is a limiting factor in our study. On the other hand, we highlighted the characteristics of strictures that require complex treatment in tertiary centers.

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Sažetak

ETIOLOGIJA STRIKTURE URETRE: ISKUSTVO TERCIJARNOG CENTRA

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Striktura uretre složena je bolest nedovoljno proučene etiologije. Učestalost etioloških čimbenika strikture uretre značajno se promijenila u posljednjih nekoliko desetljeća, imajući u vidu geografske čimbenike, socioekonomske karakteristike stanovništva te različite etiološke čimbenike prisutne u razvijenim zemljama i zemljama u razvoju. Retrospektivno smo prikupili podatke od 146 pacijenata koji su podvrgnuti uretroplastici zbog strikture uretre od 2009. do 2019. godine u Univerzitetskom kliničkom centru Srbije (Beograd, Srbija). Bolesnici sa strikturom uretre podijeljeni su u nekoliko skupina prema dobi i lokalizaciji strikture. Utvrđeno je 11 uzroka striktura uretre. Kateterizacija uretre bila je glavni uzrok striktura, bez obzira na dob, prisutna u 48.6% bolesnika ($p<0.001$). Najčešća lokalizacija bila je penilna uretra, prisutna u 41.8% bolesnika ($p<0.001$), dok su strikture posteriorne uretre uočene u samo 5 bolesnika (3.4%). S obzirom na etiologiju, prvo mjesto zauzimaju jatrogena (kateterizacija) i idiopatska uretralna stenoza. Pažljiva manipulacija uretre u procesu kateterizacije ključan je korak koji doprinosi prevenciji najčešćeg etiološkog čimbenika strikture uretre.

Ključne riječi: *Kateterizacija*; *Epidemiologija*; *Etiologija*; *Striktura*; *Uretra*; *Uretroplastika*