Review Article

Current management of urethral stricture disease

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ABSTRACT

Introduction: Broadly defined, urethral strictures are narrowing of the urethral lumen that is surrounded by corpus spongiosum, i.e., urethral meatus through the bulbar urethra. Urethral stenosis is narrowing of the posterior urethra, i.e., membranous urethra through bladder neck/prostate junction, which is not enveloped by corpus spongiosum. The disease has significant quality of life ramifications because many times younger patients are affected by this compared to many other urological diseases.

Methods: A review of the scientific literature concerning urethral stricture, stenosis, treatment, and outcomes was performed using Medline and PubMed (U.S. National Library of Medicine and the National Institutes of Health). Abstracts from scientific meetings were included in this review.

Results: There is level 3 evidence regarding the etiology and epidemiology of urethral strictures, stenoses, and pelvic fracture urethral injuries. Outcomes data from literature regarding intervention for urethral stricture are largely limited to level 3 evidence and expert opinion. There is a single level 1 study comparing urethral dilation and direct vision internal urethrotomy. Urethroplasty outcomes data are limited to level 3 case series.

Conclusions: Progress is being made toward consistent terminology, and nomenclature which will, in turn, help to standardize treatment within the field of urology. Treatment for urethral stricture and stenosis remains inconsistent between reconstructive and nonreconstructive urologists due to varying treatment algorithms and approaches to disease management. Tissue engineering appears to be future for reconstructive urethral surgery with reports demonstrating feasibility in the use of different tissue substitutes and grafts.

Key words: Stricture, tissue engineering, urethra

INTRODUCTION

Male urethral stricture disease is a common condition which results in narrowing or obliteration of the urethral lumen and may involve any segment of the urethra from the urethral meatus to the bladder neck. This is a relatively common condition which results in 1.5 million physician office visits in the US over a 9 years period from 1992 to 2000.[1] The cost of disease treatment is not insignificant, and urethral strictures resulted in $191 million in health care expenditures and resulted in approximately 5000 inpatient hospital visits in 2000 in the US.[1] Most patients present with a spectrum of symptoms; however, obstructive lower urinary tract symptoms are the most common. Furthermore, numerous sequelae such as bladder calculi, recurrent infection, fistula, and chronic renal insufficiency can result from untreated urethral stricture disease and significantly affect patient quality of life.[2]

Approximately 50% of urethral strictures occur in the bulbar urethra, 30% in the penile urethra, and the remainder in a combination of the two.[3] Urethral stenosis accounts for <15 of urethral narrowing.[3,4] This article will focus on the classification, etiology, epidemiology, pathogenesis, clinical presentation and treatment, and

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technological advances in the field of reconstructive urology.

DEFINITION

Urethral stricture is the preferred term for narrowing of a segment of the urethra which is surrounded by corpus spongiosum, i.e., urethral meatus to bulbar urethra.[5] Both the World Health Organization and the Society International d' Urologie (SIU) in a recent International Consultation on Urological Diseases (ICUD) working group have recommended that the urethra should be described in specific anatomic terms rather than anterior and posterior segments.[5] The severity of a urethral stricture is related to the amount of damage to the corpus spongiosum, the investing vascular layer of the urethra, resulting in a progressive process termed spongiofibrosis.[6] Urethral stenosis is the term for narrowing of the urethra lumen that is not surrounded by corpus spongiosum, specifically the membranous and prostatic urethra.[5] Usually, the stenosis is not progressive, like spongiofibrosis, and the extent of obliteration or narrowing of the lumen determined at the time of the traumatic or iatrogenic insult.

EPIDEMIOLOGY

The prevalence of urethral stricture disease in the US is estimated between approximately 200/100,000 in younger men to >600/100,000 in men older than 65.[1] The prevalence of urethral stricture disease in the UK has been estimated between 10/100,000 in younger men to 100/100,000 in men older than 65.[7] Medicare data in the US indicated an incidence of 0.9% in 2001, although the true incidence is not known.[8] All data show an increase incidence with advancing age with the most dramatic increase after age 65.

ETIOLOGY

Urethral stricture is divided into four major etiologies: Idiopathic, iatrogenic, inflammatory, and traumatic [Table 1].[9] Idiopathic and iatrogenic causes for urethral strictures are more common in the developed world, and each accounts for 33% of patients, respectively. Inflammatory and traumatic causes account for 15% and 19% of strictures, respectively.[9] Urethral stenosis is less well-categorized. Idiopathic strictures occur more commonly in the bulbar urethra and are more frequent in younger versus older patients (48% vs. 23%).[3,7] These may arise from unrecognized childhood trauma or a congenital anomaly in urethral development.[5] In the older patients, decreased tissue blood supply and ischemia have been proposed as a possible mechanism.[7] In the posterior urethra, idiopathic stenosis is less common and occurs in 0–2.7% of patients.[4,9] Iatrogenic urethral strictures are found from the meatus to the bladder neck. In younger patients, these strictures occur in the penile urethra or meatus and are a complication of hypospadias surgery occurring in approximately 10% of patients.[5] In older patients, the cause is transurethral surgery or long-term indwelling urethral catheters. Stenosis of the posterior urethra occurs in 5–10% of patients and is the result of prostate surgery or intervention for prostate cancer. Recent studies by Palminteri *et al*. show that 25% of posterior urethral stenosis are the result of iatrogenic intervention, and 93% of these are due to prostatectomy or radiation therapy.[3,10]

Table 1: Meta-analysis of urethral stricture etiology

Series	Number	Etiology			
		Idiopathic	Iatrogenic	Inflammatory	Traumatic
Wessells and McAninch	40	5	12	13	10
Wessells *et al*.	25	0	11	9	5
Andrich and Mundy	83	35	38	7	1
Santucci *et al*.	168	64	24	12	68
Elliott *et al*.	60	37	9	7	7
Andrich *et al*.	162	38	84	23	17
Fenton *et al*.	194	65	63	38	28
Total	732	244	241	109	136

Adapted from Fenton *et al*.[9]

Inflammatory stricture refers to a postinfectious inflammatory reaction where the urethral lumen is narrowed and accounts for about 15% of urethral strictures in the industrialized world.[5,7,9] This etiology is more common in the nonindustrialized world. A more frequent cause of inflammatory strictures in Western countries is lichen sclerosis and is the source of 5–14% of urethral strictures.[5,7,11] Inflammatory strictures are limited to the anterior urethra and are not a source of posterior urethral stenosis. Traumatic injury accounts for approximately 19% of urethral stricture or stenosis.[4,9] The most frequently injured segment of the anterior urethra is the bulbar urethra; the result of blunt straddle injury compress the urethra against the pubic symphysis.[12,13] This is rarely associated with pelvic fracture and may not be diagnosed acutely at the time of injury. The penile urethra is rarely injured, due to the mobility of the penis, but may be damaged at the time of penile fracture in 3–20% of cases.[14,15] Traumatic posterior urethral stenoses are the result of pelvic fracture urethral injury (PFUI). Greater than 70% of posterior urethral stenosis are associated with pelvic fracture, although only 3–25% of pelvic fractures are associated with urethral injuries.[16,17]

PATHOGENESIS

The pathologic change associated with urethral stricture disease is fibrosis of the epithelial-lined cavernous tissue.[7]

The urethral lumen narrows as the corpus spongiosum contracts with scar formation. The damaged urethral epithelium changes to stratified squamous epithelium which is less resilient to pressure changes and normal urethral distention. This becomes a vicious cycle with the nondistensible, nonelastic fibrotic tissue further damaged from the hydrostatic pressure of avoiding causing worsening fibrosis. Spongiofibrosis is exacerbated by tears and fissures of the metaplastic epithelium allowing urine to leak into the underlying corpus spongiosum.[6] The process progresses either longitudinally along the urethra or circumferentially into the surrounding structures. Posterior urethral stenosis is typically an obliterative process related to the traumatic injury and subsequent fibrosis secondary to urethral disruption.[18]

CLINICAL EVALUATION

There is no definite consensus on the best study for evaluation of urethral strictures.[19] Typically, three key pieces of information are needed for treatment of a urethral stricture or stenosis: Location of the obstruction, length of the obstruction, and associated urethral pathology.[18] A recent consensus panel recommended dynamic retrograde urethrogram (RUG) as a reliable method to stage and diagnose urethral stricture or stenosis.[19] This study has a sensitivity of 75–100% and a specificity of 72–97%.[19,20] Cystoscopy is recommended as the most specific test to diagnose a urethral stricture and adjunct test for staging. Voiding cystourethrogram is recommended as an adjunct study to evaluate the bladder neck and posterior urethra, especially in the setting of posterior urethral stenosis with obliteration of the urethral lumen.[19] Urethral ultrasonography has greater sensitivity in the evaluation of stricture length, diameter, and degree of spongiofibrosis compared to RUG; however, this is recommended as an adjunct study to RUG.[19,21]

MANAGEMENT

Dilation

Urethral stricture or stenosis is frequently managed with either serial urethral dilation, such as filiform and followers or urethral sounds, or radial dilation, such as balloon dilation.[22] The goal of urethral dilation is to stretch the scar without tearing the mucosa allowing a gradual enlargement in the urethral lumen. A recent Cochrane review shows multiple low-quality studies evaluating self-dilation, and there is no recommendation for its use or even which patients are appropriate.[23] One randomized study has evaluated urethral dilation versus direct vision internal urethrotomy (DVIU) and showed no statistically significant difference in outcomes between the two procedures.[24] In this study, 106 men underwent dilation, and 104 men underwent DVIU. The overall recurrence rate for dilation at 48 months was 60% compared with 50% recurrence rate for DVIU at the same time interval; however, statistical analysis revealed no significance between the two groups.

Direct vision internal urethrotomy

Incision of urethral stricture continues to be the predominant treatment of this disease, and a recent study reveals that 82.5% of board certified urologists in the US treat urethral strictures by DVIU.[22,25] Only 0.7% of urethral reconstructive urologists perform any significant number of DVIUs.[22] Most literature supporting DVIU is level 3 evidence composed of reviews series evaluating short-term outcomes with success rates ranging from 22% to 100%.[22] More recent data indicate a much lower success rate of 8–9% at 1–3 years, and overall long-term success rates appear to be 20–30%.[26] Strictures which respond better to DVIU are those <1 cm in length, located in the bulbar urethra, and have a larger urethral lumen at the time of treatment.

Repeat direct vision internal urethrotomy

Patients who do not respond to repeat DVIU are those with long strictures (>2 cm), penile strictures or membranous stenosis, or those patients with multiple strictures. Strictures which recur <3 months following treatment with DVIU have a stricture-free rate of 30% at 2 years and 0% at 4 years.[27] Patients undergoing ≥3 DVIUs have a 100% failure rate.[28]

Augmentations for direct vision internal urethrotomy

Many strategies have been employed to improve the success rate for DVIU in the management of urethral stricture. There is a conflicting data regarding intermittent catheterization (IC), and if it reduces time to recurrence, however, IC necessitates continued urethral instrumentation and increases the likelihood of progression of the initial stricture.[22,23] Patients who perform IC have a greater chance of complication (urinary tract infection, infection, bleeding, etc.,). Injection agents have also been evaluated in an effort to improve DVIU outcomes. Mitomycin C injection has been evaluated by multiple investigators with some studies showing excellent outcomes on recalcitrant strictures while others have shown only modest improvements.[29,30] Triamcinolone injected at time of DVIU has been shown to decrease stricture recurrence from 50% to 21%.[31]

Laser urethrotomy has been evaluated, and this technique does not show any superiority to standard techniques for DVIU, regardless of energy source, and has a higher complication rate.

Complications of direct vision internal urethrotomy

The most common complication of DVIU is urethral bleeding and perineal hematoma with the incidence of each of these findings symptoms at about 20%. Long-term complications include erectile dysfunction, in 2–10% of patients, and recurrence of stricture.[22] Complications are most common in patients with a long stricture, stricture of the penile urethra, positive urine culture, and multiple strictures.[2]

Urethroplasty

Most reconstructive surgeons consider urethroplasty to be the gold standard for management of urethral stricture and stenosis.[32] Current data for both excisional urethroplasty and use of grafts show higher long-term success rates than any other form of management of urethral strictures. In fact, multiple studies have evaluated cost-effectiveness of treatment of urethral strictures and found that either immediate urethroplasty or a single attempt at DVIU, followed by urethroplasty for failures, was more cost-effective than long-term dilation, or DVIU with urethroplasty used only for salvage procedures.

Excision and primary anastomosis

Excision and primary anastomosis (EPA) is the excision of the urethral scar and reconnection of the urethra. A recent SIU/ICUD consultation on urethral strictures noted that EPA should be considered the optimal treatment for short bulbar urethral strictures regardless of etiology or previous treatment.[32] This technique is used most often on strictures 2 cm or less and has excellent success rates of 90–95% long-term.[32] In general, the complication rate of EPA is low, <10%, and most resolve within 6–12 months.[7]

Augmented urethroplasty

The two most important considerations in urethral reconstruction are length of the urethral stricture and location. For those strictures that are longer or in anatomically unfavorable locations, i.e., penile urethra, either free grafts or pedicle flaps are necessary for urethroplasty.[33] Prior to the introduction of oral mucosa grafts in the 1990s, all augmented urethral reconstruction was performed with skin flaps or grafts in one or two stages.[34] This tissue has excellent microvascular architecture, via extensive vascular arborization in the lamina propria, making it a robust graft material. A review of graft placement location shows a success rate of approximately 88% at 3 years for both dorsal and ventral onlay techniques, and multiple techniques have similar results [Table 2].[33] The urethral stricture recurrence rate for both flaps and grafts is similar around 14.5–15.7%.[34] Once the most popular technique, pedicle skin flaps have become less common owing to their more complex harvest and complications. The long-term success rates of skin flaps are 73–90.5%[35] [Figures 1 and 2].

Table 2: Meta-analysis of oral graft onlay techniques

Technique	Number of patients (*n*)	Follow-up (months)	Success rate (%)
Dorsal onlay bulbar	934	42.2	88.3
Ventral onlay bulbar	563	34.4	88.8
Lateral onlay bulbar	6	77	83
Asopa	89	28.9	86.7
Palminteri	53	21.9	90.6
One-stage penile	432	32.8	75.6
Two-stage penile	129	22.2	90.5
Panurethral	240	30.1	88.2

Adapted from Chapple *et al*.[33]

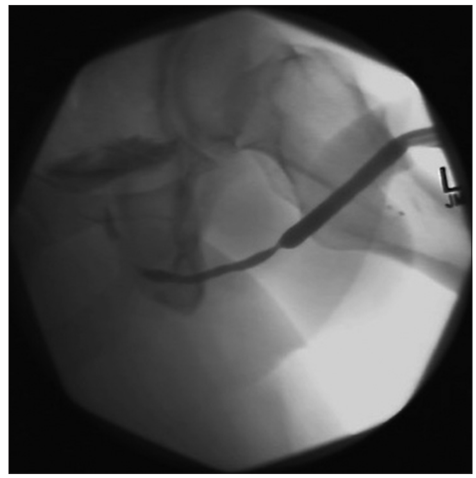

Figure 1: Preoperative retrograde urethrogram showing bulbar urethral stricture

Posterior urethroplasty

As previously discussed, narrowing of the posterior urethra is termed stenosis and is the result of PFUI.[17] These conditions are often managed through excision of the scar tissue and reanastomosis of the healthy urethral segments, although, some patients may undergo successful primary urethral realignment at the time of injury. Historically, this technique used crude methods such as interlocking sounds; however, with the advent of flexible endoscopes, this technique is more refined. The long-term outcomes from this procedure are mixed with some authors showing excellent success rates as high as 76%, and others much lower at 21% long-term success.[36,37] Due to this variability in outcome, there is no consensus among reconstructive surgeons as to the indications and utilization of this technique. As the PFUI is often associated with significant hematoma and postinjury inflammation, the repair is usually delayed 3–6 months after injury.[12] Multiple steps may be required to complete a tension-free anastomosis including extensive urethral mobilization, division of the crus of the corpora cavernosa, inferior pubectomy, and corporal rerouting of the urethra lateral to one crus of the corpora cavernosa. The primary complications associated with both the injury itself, and the surgical management includes erectile dysfunction and urinary incontinence. Due to the force of injury, many patients have preoperative erectile dysfunction, so it is difficult to determine the exact percentage of patients developing this complication de novo from surgery. Despite injury or obliteration of the membranous urethra, continence is maintained at the level of the bladder neck.[17] With appropriate preoperative evaluation and surgical technique, the success rate of this

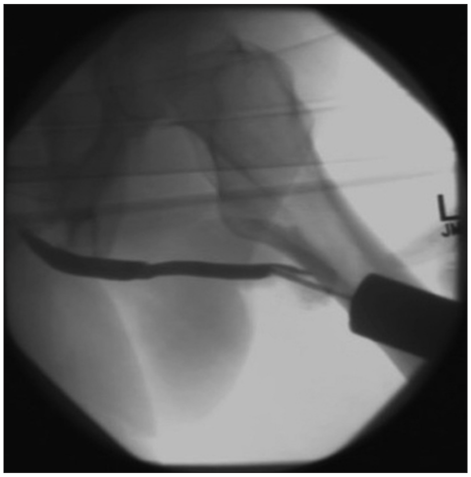

Figure 2: Postoperative retrograde urethrogram showing resolution of stricture following augmentation urethroplasty with buccal mucosa graft

technique is approximately 90–98%. Some of these series include adjuvant DVIU to achieve success.[12,17]

Quality of life outcomes

The overall success rates for urethral reconstruction of various anatomic urethral strictures or stenosis using different surgical techniques is well-documented and consistent among studies. What is less well-described and understood is patient quality of life outcomes, including sexual function. Temporary erectile dysfunction is a known complication following anterior urethroplasty and may occur in up to 38% of men following urethroplasty with the highest incidence following bulbar urethroplasty.[38,39] This typically resolves within 6–12 months of surgery without further sequelae. Ejaculatory function is less described. In the limited studies performed, a minority of men complain of ejaculatory function preoperatively (25%), and this improves postoperatively in up to 36% of men.[40] Only two validated outcome measure instruments exist, for evaluating patient-viewed outcomes from urethral reconstruction.[41,42] The instrument developed by Jackson *et al.* relates to a larger spectrum of urethral reconstruction outcomes and is undergoing full external validation. These instruments are important to better define patient-related outcomes and quality of life which are the best measure of success following reconstructive surgery.

FUTURE DIRECTIONS

Changes in the field of reconstruction focus on management approach and graft material. The most important trend in the field of urethral reconstruction is the shift toward surgical reconstructive techniques that lead to cure of disease and away from maintenance procedures, such as dilation and repeat DVIU. One area of future impact is well-designed prospective, clinical research instead of large retrospective, single institution clinical series. A challenge when managing conditions such as urethral stricture disease, versus malignancies, is that quality of life becomes one of the dominant outcome measures. One step forward in this regard is the introduction of validated outcome measures.[43] In addition, others groups, such as the Trauma Urologic Network of Surgeons, have evaluated standard outcome measures in a multi-institutional setting.[44] Furthermore, evaluation of standard outcome measures, such as questionnaires, quantitative measures, i.e., flow-rate, and visual inspection allows other reconstructive surgeons to "benchmark" their results to ensure that their outcomes are comparable to these cross-sectional data. The next major advance in urology will likely come from the fields of tissue engineering and stem cell therapy. The simplest form of tissue engineering involves the use of acellular matrices (AM).[45] AMs are essentially bioscaffolds composed of collagen, elastin, and glycosaminoglycan.[45] There are multiple methods to create the acellular structures, but most are or biologic origin, i.e., derived from animal or human sources and differ primarily on the amount of collagen and extracellular matrix present. The current utility of these products is that they can be used "off the shelf" and do not require harvesting. Several studies from Brazil have used urethral acellular matrix grafts in human subjects with encouraging results.[45] These grafts were placed using both a dorsal and ventral onlay technique. What is surprising is that these engineered products produced results similar to oral mucosa grafts [Table 3]. A noted limitation for these AMs is distance to native urothelial tissue. Most studies conclude that the maximum extent of cellular ingrowth is approximately 1–1.5 cm from the urethral epithelium. The potential future use of cell-seeded matrices may eliminate this limitation and improve outcomes. The other current engineered tissue being evaluated is tissue-engineered buccal mucosa.[46] In this application, the native oral mucosa from the patient is cultured and grown on a cadaveric dermal scaffold which is devoid of the epidermis. A biopsy of the oral mucosa is obtained and used to create a "sheet" of tissue on the scaffold. This process takes approximately 2 weeks, for a healthy sheet of tissue to be created. This process has been evaluated favorably with midterm results showing an 83% success rate.[46] This compares favorably with buccal mucosa harvested at the time of urethroplasty and used for urethral augmentation. This success has moved some to consider this a standard reconstructive tool and use this process regularly. The final advancement not yet reached is the use of stem cells for urethral reconstruction. Stem cells are unique in that they can regenerate and self-renew and differentiate into a number of different cell types, including all layers of a structure such as the urethra. Stem cells have been effectively used in other urologic applications including voiding dysfunction, urinary incontinence, and erectile dysfunction.[47] Stem cells have multiple effects. In addition to being progenitor tissue cells, they can also be used for autocrine and paracrine function. These cells are referred

Table 3: Meta-analysis of human biologic acellular matrices

Series	Year	Source	Cell-seeded	Stricture length (cm)	Onlay approach	Follow-up (months)	Success rate (%)
Mantovani	2002	SIS	No	3-10	Dorsal	6	5/5 (100)
Ribeiro-Filho	2006	Human urethra	No	3-18	Ventral	25	7/7 (100)
Donkov	2006	SIS	No	4-6	Dorsal	18	8/9 (89)
Hauser	2006	SIS	No	3.5-10	Ventral	12	1/5 (20)
Palminteri	2007	SIS	No	2-8	Dorsal/ventral	21	17/20 (85)
Fiala	2007	SIS	No	4-14	Not described	31	40/40 (80)
Fossum	2007	Dermis	Yes	4-6	Not described	60	3/6 (50)
el-Kassaby	2008	Bladder	No	2-18	Ventral	25	8/9 (89)
Bhargava	2008	Dermis	Yes	5-11	Not described	33	3/5 (60)
Mantovani	2011	SIS	No	3-10	Ventral	120	40/40 (100)
Palminteri	2012	SIS	No	2-8	Dorsal/ventral	71	19/25 (76)
Ribeiro-Filho	2014	Human urethra	No	3-18	Ventral	42	33/44 (75)
Total							184/215 (85.6)

Adapted from Ribeiro-Filho and Sievert.[38] SIS: Small intestinal submucosa

to as secretomes and function to encourage cell growth and differentiation.[47] While this application has been used in wound healing, the cells used are mesenchymal stem cells, and while performing some secretory functions, the cells do not engraft into the injured tissue and cannot completely regenerate the affected body structures. If these unique stem cells or secretomes can be used to better heal damaged tissues or structures, such as the urethra, significantly less invasive procedures could be used to reconstruct urethral strictures or stenosis.

CONCLUSION

Urethral strictures are a frequent problem that many urologists encounter. The classification and nomenclature of urethral strictures has been recently standardized, bringing greater uniformity to their study and treatment. The predominant age group suffering from this disease is older men, and the most common cause, in industrialized countries, is iatrogenic. As the severity of disease depends on the degree of spongiofibrosis, treatment of urethral strictures is varied. Currently, urologists are moving away from maintenance, i.e., dilation and DVIU, toward management, i.e., urethroplasty. Options for management of urethral stricture include EPA and augmented urethroplasty, most commonly with buccal mucosa grafts, and the choice of technique is dependent on the anatomic location within the urethra and length of the stricture. Evaluation and application of tissue engineering to urethral reconstruction have opened new avenues to treatment options using acellular and cellular tissue matrices. Other future therapies still awaiting transition from the laboratory to the clinical setting are the use of stem cells and secretomes. With each progression in the field of urethral reconstruction, the ultimate goal remains to create a successful, durable outcome, while maximizing patient quality of life.

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Conflicts of interest

There are no conflicts of interest.

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