

Current trend in the management of male urethral stricture disease: A review of literature with future directions

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Abstract

Urethral stricture disease is a common urological problem in men with increasing incidence and if left untreated it may result into various life threatening complications. The exact role of CT scan and MRI is yet to be defined. Majority of urologists consider urethroplasty as 'gold standard' treatment in the management of urethral stricture. However, to date the excision of diseased urethra and use of graft in urethroplasty has long-term success. The studies evaluating cost factors suggest that either an immediate urethroplasty or a single attempt at internal urethrotomy followed by urethroplasty is cost-effective. Obviously, the trend is toward treatment using reconstructive procedure which cures stricture disease without maintenance procedure e.g. dilation and repeat internal urethrotomy. EPA or augmented urethroplasty using buccal mucosa graft (BMG) are most commonly done procedures. American Urological Association (AUA) symptoms score and uroflometry (UFM) are more useful in the follow up of different urethroplasty. The application of tissue engineering methods has opened a new avenue in the treatment in urethral stricture with stem cells and secretomes awaiting transition from laboratory to clinical use.

Keywords: Urethra, LUTS, UTI, Spongiofibrosis, Stricture, Urethroplasty, Secretomes.

Introduction

Urethral stricture disease is a common urological problem in men, which results into narrowing or obliteration of urethral lumen.¹ It can involve any segment of urethra from meatus to bladder neck. Majority of patients present with the spectrum of symptoms but clinical presentation with obstructive lower urinary symptoms (LUTS) is common. According to one report, this common condition resulted into 1.5 million physician visits during between year 1992-2000 with approximately 191 million dollar health care expenditure and about 5000 indoor visits in USA.² Further, the untreated urethral stricture disease may also develop various complications including recurrent urinary tract infection (UTI), bladder calculi formation, development of fistula and chronic renal failure, which may significantly affecting quality of life.³

Almost, 50% of urethral stricture occurs in bulbar part, 30% in penile and rest may involve a combination of various parts.⁴ This article will focus on the current classification, epidemiology, etiology, pathogenesis and clinical evaluation in the management of urethral stricture disease and potential future treatments.

Definition

Urethral stricture is preferred term for narrowing/obliteration of urethral lumen surrounded by the corpus spongiosum from urethral meatus to bulbar urethra.^{5,6} It has been stressed by the World Health Organization (WHO) as well as the Society International d'Urologie (SIU) that all the urethral stricture should be described in terms of its specific anatomical segments in lieu of either anterior or posterior urethral stricture. Severity of urethral strictures depends on the amount of damage to corpus spongiosum which leads into a progressive process called 'spongiofibrosis'.⁷ On other hand, the urethral stenosis is term used for narrowing/obliteration

of the urethral segment not surrounded by corpus spongiosum i.e. membranous and prostatic urethra which being non-progressive and its extent is determined by severity of injury.⁶

Epidemiology

Prevalence of urethral stricture disease is about 200 cases per 100,000 population in young men and about 600 cases per 100,000 population in men aged > 65 years in USA compared to 10 cases per 100,000 population and 100 cases per 100,000 population in the same age group in UK, respectively.⁸ Data from USA suggest that overall incidence was about 0.9% in 2001 year and true incidence still remains unknown.⁹ However, the current data suggests that a dramatic increase in incidence occurs in the men with advanced age groups.

Etiology

According to etiological causes, urethral strictures disease may be classified into 04 major groups which includes idiopathic, iatrogenic, inflammatory and traumatic (Table 1).¹⁰ In developed nations, idiopathic and iatrogenic causes are more frequent and accounts for about 33% cases each. Inflammatory and traumatic urethral strictures represent about 15-19% of cases, respectively.⁹ To date, urethral stenosis remains a less well categorized disease. Idiopathic strictures occurs more commonly in bulbar part and atleast twice more frequently in younger compared to older men (48% vs. 23%).^{5,8,9} Urethral stricture also occurs following unrecognized trauma during childhood or due to maldevelopment of urethra. The possible mechanisms for development of urethral stricture in older men include decreased blood supply to urethra and tissue ischemia. Idiopathic stenosis in the posterior urethra is less common and occurs in about 2.7% of cases.¹⁰ Iatrogenic urethral stricture may develop from urethral meatus to bladder neck.

Table 1: Meta-analysis of etiology of urethral strictures.

Various Series, number of patient & their etiological cause					
	(n=)	Idiopathic	Iatrogenic	Inflammatory	Traumatic
Wessells & Mc Aninch	40	5	12	13	10
Wessells <i>et al</i>	25	0	11	9	5
Andrich & Mundy	83	35	38	7	5
Santucci <i>et al.</i>	168	64	24	12	68
Elliott <i>et al.</i>	60	37	9	7	7
Andrich <i>et al.</i>	162	38	84	23	17
Fenton <i>et al.</i>	194	65	63	38	28
Total	732	244	241	109	136

In younger men, iatrogenic stricture occurs in penile urethra or meatus, usually due to complication of hypospadias surgery in 10%. However, in older men, the usual cause is transurethral surgery or prolonged indwelling urethral catheters.⁶ Posterior urethral stenosis occur in about 5-10% of cases as result of either prostate surgery or intervention for prostate cancer. Data suggests that about 25% of posterior urethral stenosis occur due to iatrogenic causes, 93% developing after prostatectomy or radiotherapy.^{5,10}

Inflammatory stricture referred to post-infection inflammatory reaction also causes narrowing of urethral lumen. These strictures are more common in non-industrialized World but about 15% of such cases also occurs in the industrialized World.^{6,7,9} Another cause of inflammatory stricture development in the industrialized World is lichen sclerosis (LS), which is responsible for about 5-14% of cases.^{6,7,12} Usually, the inflammatory strictures are confined to anterior part of urethra and do not leads to posterior urethral stenosis.

Traumatic injury accounts for about 19% of urethral stricture or stenosis.^{4,9} Bulbar urethra is most frequently involved part, the blunt straddle injury stretches bulbar urethra against pubic symphysis and rarely associated fracture pelvic may be not diagnosed at the time of initial injury.^{13,14} Penile urethra is uncommonly during pelvic fracture due to its mobility but injury can occurs in about 3-20% cases.^{15,16} Usually, posterior urethral stenosis results from pelvic fracture urethral distraction injury (PFUI) in $\geq$ 70% cases concomitant with pelvic fracture but only about 3-25% of pelvic fractures are associated with urethral injury.^{17,18}

Pathogenesis

Pathological change associated with urethral stricture disease includes fibrosis of epithelial lined spongiosum tissue. Urethral lumen is narrowed as the corpus spongiosum tissue contract with scar formation and damaged urethral epithelium changes into stratified squamous epithelium, which is less resilient to hydrostatic pressure change and normal urethral distension. Ultimately, a vicious cycle of non-distension, non-elastic and fibrotic process leads to further damage from hydrostatic pressure of voiding, causing worsening of fibrosis. Spongiofibrosis is further exacerbated by tears and fissures in the metaplastic epithelium which allow urine leakage into underlying corpus spongiosum.⁶

This process may progress either in the longitudinally direction along urethra or circumferentially into surrounding tissue. Posterior urethral stenosis is typically an obliterative process, related to trauma and subsequent development of fibrosis due to secondary urethral disruption.¹⁸

Clinical Evaluation

A. Clinical Assessment

Evaluation of urethral strictures require proper assessment of the severity of symptoms, impact on the quality of life (QoL) and identification of causative factors in patient. Majority of patients present with voiding LUTS, sense of incomplete voiding and as obstruction progress with or without haematuria or UTI. A combination of American Urological Association (AUA) symptoms score and objective parameter such as uroflowmetry (UFM) may be used to compare outcomes of different types of urethroplasty.¹⁰ UFM typically shows a plateau pattern with low Qmax. The effective caliber of unobstructed urethra is 11 Fr in the presence of normal functioning bladder in men. However, UFM alone may not be able to diagnose urethral stricture until a significant narrowing of urethral lumen has occurred to less than 11 Fr size.¹²

B. Urethrography

Retrograde urethrography (RUG) provides key information about urethral strictures in terms its location, length and associated pathology affecting urethra (e.g. diverticulum, fistula, false passages) which aids in the planning of appropriate urethroplasty. When suprapubic catheter (SPC) is lying in situ, an antegrade urethrography may be performed. However, a synchronous RUG with voiding cystourethrogram (VCUG) done through the suprapubic catheter with cystoscopy (either retrograde or antegrade) is recommended test to assess posterior urethral stricture and the bladder neck function, which might have implications in PFUI.

C. Cystourethroscopy

Flexible or rigid urethroscopy is most recommended specific test for assessing location, degree of severity and urethra lumen distal to stricture. Urethroscopy may also be employed in the follow up of patients who has undergone urethroplasty because UFM alone may not be able to diagnose recurrence until the urethral lumen has obliterated to a significant

extent.^{12,13} Urethroscopy also has role in the early catheter realignment during acute management of high grade PFUI.¹⁴

D. Imagings

Ultrasonography (USG) may be helpful in assessing length and degree of spongiofibrosis but not recommended as sole test of imaging. It should always be combined with urethrography due to its anatomical limitations.¹⁵ Data regarding routine use of Color Doppler USG for preoperative assessment of erectile dysfunction (ED) is conflicting. CT scan and MRI may provide useful information, especially in the patients of PFUI to identify injury not demonstrated by conventional imaging.¹⁶

Management

1. Urethrotomy and Dilation

Direct visual internal urethrotomy (DVIU) or optical internal urethrotomy (OIU) continued to remain a predominant method of treatment and even about 82.5% board certified urologists in USA are still using this method to treat urethral stricture disease. However, only 0.7% reconstructive urologists performs significant number of DVIU.²² The intention of urethral dilatation is to stretch the scar of stricture in order to restore its caliber with the hope that it might heal open, provided there is adequate urethral blood supply. Both techniques offer almost equal stricture free rate (SFR) of about 50% in selected patients, which is significantly lower to urethroplasty which may having SFR of about 90-95%. Majority of urologists prefer one attempt at DVIU in single, short, soft bulbar stricture of length < 1cm and second attempt is offered to only those patients who develop recurrence after 6 month of initial treatment. Repeat DVIU has limited efficacy unless combined with the long-term intermittent self dilatation and its duration has not been defined.^{30,31} There is level-3 evidence available to this in the form of review of cases series. Recent data indicate even much lower success rate of 8-9% at 1- 3 years with long-term success rate of about 20-30%.²⁶ Patients with long stricture $\geq$ 2cm, penile stricture, membranous stenosis and multiple strictures do not respond to DVIU. In healthy patient, the stricture recurrence within 3 month after initial DVIU/Dilatation or those who failed second attempted at DVIU, further attempts remain only palliative.³⁴ Uses of various agents (e.g. mitomycin-c, triamcinolone, collagenase) to improve the outcome of DVIU has resulted into only modest increase in success rate.^{29,30}

Recently used, laser urethrotomy is not superior to conventional OIU and also has higher rate of complications. Most common complication of OIU is urethral bleeding and perineal hematoma, which may occur in about 20%.of cases. Long-term complications includes erectile dysfunction in 2-10% and recurrence in 50%.²² Complications are more common in the patients of long stricture segment, penile urethral stricture and multiple urethral stricture disease with positive urine culture.²

Use of urethral stent as temporary and permanent method for treatment of anterior stricture is associated with

significant complications e.g. perineal discomfort, painful erection and recurrence.³⁵

2. Urethroplasty

Majority of reconstructive urologists consider urethroplasty as 'gold standard' treatment in the management of urethral stricture and stenosis.³² Excision of diseased urethra and use of graft in urethroplasty has more long-term success rate. The studies evaluating cost factors suggest that either an immediate urethroplasty or a single attempt at DVIU followed by definite urethroplasty is more cost-effective.

A) Excision & primary anastomosis (EPA)

EPA is complete excision of urethral scar tissue and anastomosis of healthy, pink, bleeding urethra ends. Recent consultation on urethral stricture managements has recommended EPA as optimal method of treatment for short length bulbar strictures, regardless of its etiology or previous treatment.³² This technique has excellent long-term success rates of about 90-95% for urethral strictures $\leq$ 2 cm.³² Complication rate is also less than 10% and majority of them resolving within 6-12 month period.⁷

B) Augmented Urethroplasty

Two most important factors for reconstruction of urethral stricture are its length and location. Urethral strictures longer than 2 cm or located in the unfavourable locations (e.g. penile urethra) require free graft or pedicle flaps for reconstruction.³³ Before, the introduction of buccal mucosa graft (BMG) in year 1990, all the augmented urethral reconstruction used skin flap or graft in single or staged procedure.³⁴ BMG tissue has excellent microvascular architecture with extensive vascular arborisation in the lamina propria which make it a robust graft material for reconstruction of urethral stricture disease. Review of graft location in augmented urethroplasty shows that both dorsal and ventral onlay techniques have almost equal success rate of about 88% at the end of 3 years with other techniques also producing similar results (Table-2).³³ Recurrence rate of stricture for both flap and graft urethroplasty is about 14.5-15.7%.³⁴ Once popular, the pedicle skin flap technique is less common due to more complex harvesting method and associated complications. Long-term success rate for skin flaps is about 73-90.5%.³⁵

C) Posterior Urethroplasty

As discussed earlier, the narrowing of posterior urethra is termed as urethral stenosis and it commonly results from PFUI.¹⁷ Posterior urethral stenosis is often managed by excision of scarred tissue and reanastomosis of healthy urethral segments; some may be successful managed by primary urethral realignment at the time of injury. Historically, this technique used crude methods such as interlocking metal sounds.

Table 2: Meta-analysis of BMG-onlay urethroplasty techniques.

Techniques	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

With the advent of flexible endoscopes, this technique has been further refined. Overall, the procedure has mixed outcomes, although some authors have reported excellent long-term outcomes with success rate of 76%, while other only 21% success.^{36,37} Due to variable outcomes, there is no consensus among reconstructive urologists in regards to its indications and utilization. As PFUI is often associated with significant hematoma and post-trauma inflammation, thus repair is usually delayed for about 3- 6 months period so that haematoma resolve and inflammation subsides.¹² The steps for tension-free anastomosis includes extensive urethral mobilization, division of crus of the corpora, inferior pubectomy and corporal rerouting of urethra. Primary complications associated with injury or surgical reconstruction includes erectile dysfunction and urinary incontinence. Many patients have preoperative erectile dysfunction due to force of injury. Thus, it is difficult to determine the exact incidence of this complication de novo from surgery. Usually, continence is maintained by bladder neck, despite injury or obliteration of membranous urethra.¹⁷ However, with suitable preoperative evaluations and use of surgical techniques, the success rate is about 90-98%. Some of the case series also includes adjuvant DVIU to achieve high success.^{12,17}

3. Quality of life (QoL)

Far less is known and understood about the patient's QoL in terms of sexual dysfunction. The temporary erectile dysfunction (t-ED) is known complication following anterior urethroplasty with incidence of 38% in bulbar urethroplasty, which may resolves in 6-12 months period without further sequele.^{38,39} The ejaculatory dysfunction is less well described complication. In one study, only 25% men complained of preoperative ejaculatory dysfunction which improved in upto 36% men, postoperatively.⁴⁰ Out all validated outcomes, measurement of instruments for patient's viewed outcomes. The instrument developed by Jackson et al. is undergoing full external validation.⁴¹⁻⁴⁴ This instrument defines patient's viewed QoL outcome and thus best measurement of success following reconstruction.

Future Directions

Obviously, the trend is toward use of reconstructive methods which cure stricture disease without maintenance procedure

e.g. dilation and repeat DVIU. The standard outcome measurements such as questionnaires, quantitative measurements i.e. flow-rate and visual-inspection allows other to 'benchmark' their results, ensuring that outcomes are comparable to cross-sectional data. Major advancement has come from the area of tissue engineering and stem cell therapy. The simplest form of tissue engineering involves, use of acellular matrixes (AM) which are essentially bioscaffolds composed of collagen, elastins, and glycosaminoglycans.⁴⁵ Majority of acellular structures are derived from animal or human sources, differing in amount of collagen and extracellular matrix. These products can be used "off the shelf" and do not require harvesting. A study from Brazil used urethral acellular matrix grafts placed with dorsal and ventral onlay techniques in human with result similar to BMG [Table 3].⁴⁵ One of the limitations observed in use is distance for the native urothelial tissues and the maximum extent of cellular ingrowths is about 1-1.5cm from the urethral epithelium. However, the use of cell-seeded matrices might overcome this limitation with improved results. Tissue-engineered BMG is also being evaluated and in this technique, native buccal mucosa of patient is cultured and grown on cadaveric dermal scaffold devoid of epidermis. A biopsy of buccal mucosa is taken to create a 'sheet' of tissue on scaffolds and this process take about 2 weeks time for creation of healthy sheets of tissue. The valuation of results suggest 83% success rate which is favourably comparable to buccal mucosa harvested at the time of augmentation urethroplasty.⁴⁶ Such a high success rate has led many to believe this as reconstructive procedure of choice with suggestion to use this technique, more frequently and regularly. However, a final advancement yet to be achieved is use of stem cells for urethral reconstruction. Stem cells are unique, as they can be regenerated, self-renewable and may differentiate into number of different cells type including all layers of urethra. Applied use of stem cells in urological conditions includes voiding dysfunction, urinary incontinence and erectile dysfunction.⁴⁷ In addition to these being progenitor tissue cells, they can be used for autocrine and paracrine functions. These cells are referred to as 'secretomes', functioning to encourage cells growth and differentiation.⁴⁷

Table 3: Meta-analysis of human biologic acellular matrices

Series	Year	Source	Cell	Stricture seeded -length	Onlay approach	Follow-up Months	Success rate
Mantovani	2002	SIS	No	3-10 cm	Dorsal	6	5/5 (100%)
Ribeiro-Filho	2006	Human urethra	No	3-18 cm	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%)							

This application is already in use for wound healings but mesenchymal stem cells while performing secretomes functions, the cells do not engraft into injured tissue or completely regenerate the affected structure. If these unique stem cells or secretomes could be used to heal the damaged tissues or structures such as urethra, then a less invasive procedure would be available for reconstruction of complex disease such as urethral stricture.

Conclusion

Urethral stricture disease is common urological problem in men. The classification and nomenclature of urethral stricture have been standardized to bring greater uniformity in the evaluation and outcome of treatment. Predominantly, older men are affected and iatrogenic cause is most common in the industrialization World. Severity of stricture depends on the degree of spongiositis and outcomes after treatment remains variable. With passage of time, more and more urologists are moving away from simple maintenance procedures to standard reconstructive urethroplasty. The EPA or augmented urethroplasty using BMG is most commonly used procedures and application of tissue engineering methods has opened a new avenue in the treatment in urethral stricture. Stem cells or secretomes are still awaiting transition from laboratory to clinical use. Still, the ultimate goal is give a successful and durable outcome to patient with best possible quality of life.

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Conflict of Interest

None.

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