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Tissue Engineering Graft for Urethral Reconstruction: Is It Ready for Clinical Application?

ABSTRACT

Despite developing surgical techniques in urethral surgery, the outcome and complications are still unsatisfactory. Alternative treatment modality has been coming up, particularly in patients with longer stricture, under revision surgery, and penile stricture. Tissue engineering grafts are a promising approach for substituting urethral reconstruction. Over the decades, numerous preclinical studies have been published to show the efficacy and safety of different origins of materials, the presence of autologous cells (acellular matrices or autologous cell-seeded matrices), and the construction of engineered tissue (patch or tubularized constructs) on animal models. However, the results of these studies have not yet reached the intended level for daily clinical practice. A PubMed database search was performed for articles, using specific keywords, published between 1998 and 2022, with a selection on using tissue-engineered grafts for urethroplasty. Many materials have been used as a graft, such as acellular bladder matrix, small intestinal submucosa, acellular dermal matrix, and polyglycolic acid with or without cells, and were evaluated according to the functional and anatomical outcomes comprising complications. According to current literature, tubularized scaffolds constructed from co-cultured cells have promising results for the future. However, high-quality evidence through randomized controlled studies with larger sample sizes, with a long-term follow-up is required to determine accurate outcomes.

Keywords: Regenerative medicine, tissue engineering, urethral stricture

Introduction

Urethral stricture (US) is a narrowing of the urethral lumen due to fibrosis of the urethral wall. These strictures can progress to symptomatic urinary tract obstruction as well as other complications, such as urinary retention, urinary tract infection, bladder calculi, and renal failure with a decreased life quality. Several factors have been reported regarding the etiology of US, including trauma, instrumentation, and infection, but most cases are idiopathic.[1] A US affects not only physical well-being but also causes psychological stress. The incidence of the disease among susceptible populations is 0.6%, totaling 5000 inpatient visits annually in the USA.[2]

The current treatment options for US include minimally invasive endoscopic management (urethral dilatation or direct visual internal urethrotomy (DVIU)) or open reconstructive surgery (urethroplasty). For stricture of the bulbar urethra with a length less than 2 cm, anastomotic urethroplasty should be considered a first-line treatment option due to its 85%–95% success rate after 1 failed dilatation or DVIU.[3,4] However, it is challenging to achieve such a high success rate for longer strictures, revision cases, and penile strictures.[5] For these cases, substitution urethroplasty allows for a wider urethral lumen caliber via the appropriate graft or flap.

Because of its lack of hair bulbs, resistance to mechanical, thermal, or chemical irritants, low donor site morbidity, and ease of harvesting grafts, the buccal mucosa has been chosen as a first graft option for the last 2 decades.[3,4] However, some patients with full-length stricture, complex urethral defect, or revision cases who underwent prior graft harvesting

Mazhar Ortac[1,2]
Teresa Olsen Ekerhult[1,3]
Weixin Zhao[1]
Anthony Atala[1]

[1]*Wake Forest Institute for Regenerative Medicine, Winston Salem, NC, USA*
[2]*Department of Urology, İstanbul University Faculty of Medicine, İstanbul, Turkey*
[3]*Department of Urology, Region Västra Götaland, Sahlgrenska University Hospital, Gothenburg, Sweden*

Corresponding author: Mazhar Ortac
✉ mortac@wakehealth.edu

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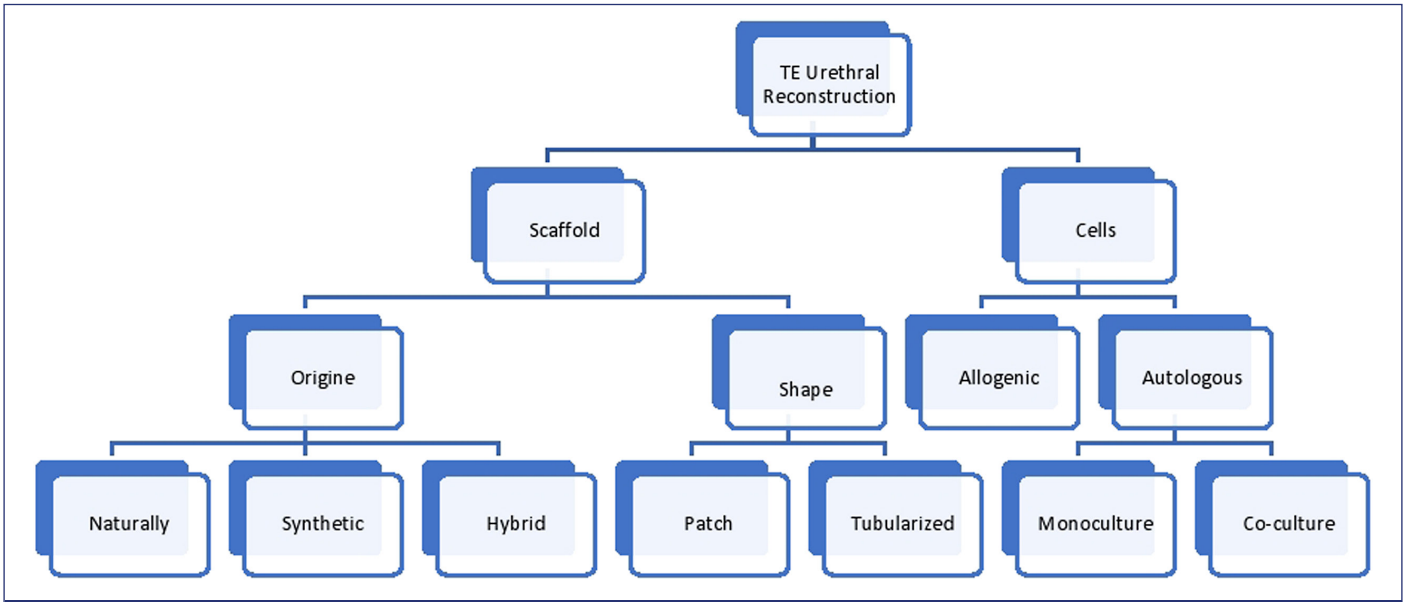

Figure 1. The type of scaffolds and cells for tissue-engineered urethral reconstruction.

require extensive grafting. Recently, tissue engineering (TE) of the urethra has focused on a different graft material to repair those conditions.[6]

New advances in the treatment of USs have commonly come from the field of regenerative medicine.[7] Preclinical studies are fundamental steps for developing new treatment options to prevent or resolve strictures (e.g., stem cells, stents, and antifibrotic agents) and to develop open urethroplasty techniques (e.g., TE).[8] Large preclinical studies have been published that investigated the outcomes of different origins of materials, the presence of autologous cells (acellular matrices or autologous cell-seeded matrices), and the construction of engineered tissue (patch or tubularized constructs) on animal models.[9]

Despite the increasing number of preclinical studies, the clinical application of TE graft urethroplasty remains limited and controversial.[10] Therefore, in this article, we review the outcomes of TE urethra in clinical studies based on contemporary literature.

Tissue Engineering of the Urethra

Tissue engineering is a technique of regenerative medicine that is defined as follows: "the principles of cell transplantation, materials science, and engineering toward the development of biological substitutes that would restore and maintain normal function."[11] The primary strategy behind TE grafts for urethroplasty is based on scaffolds and cells. While scaffolds provide structure, cells provide a barrier for resistance to mechanical or chemical irritants during urine transportation. According to the extant literature, many options are available for scaffolds and cells that can be used alone or in combination.[12] Several scaffolds have been reported, such as natural materials, synthetic polymers, and hybrid or composite scaffolds.[9] Furthermore, the scaffolds can be divided into either cell-seeded or acellular grafts (Figure 1).

MAIN POINTS

- *The outcomes of clinical studies on tissue engineering (TE) grafts remain inconclusive because of the inadequate quality of existing trials.*
- *The significant challenges related to developing TE grafts are the cost and time-consuming process of developing cell-seeded constructs.*
- *It appears that scaffolding with cells has promising results for the future.*

a. Natural material: Natural material is generally developed from cadaveric materials or animal organs. After the decellularization of the biomaterials, the remaining tissue is called an acellular matrix that contains a large amount of collagen.[9] Theoretically, the acellular matrix is considered non-immunologic and non-allergic. Bladder acellular matrix grafts,[13,14] small intestinal submucosa (SIS),[15-18] acellular corpus spongiosum matrix,[19] and acellular dermal matrix[20] have been successfully used for TE urethroplasty in preclinical and clinical studies.
b. Synthetic polymers: Synthetic polymer scaffolds for TE urethroplasty commonly use biodegradable polymers, such as polylactic acid, polylactic co-glycolic acid, poly-l-lactide-co-ε-caprolactone, polycaprolactone, and polyglycolic acid (PGA). Many synthetic scaffolds have been used in regenerative medicine for decades and are also approved by the Food and Drug Administration (FDA) for use as surgical sutures.[9,21]
c. Hybrid or composite scaffolds: Hybrid or composite scaffolds are made using a combination of natural materials and synthetic polymers. Autologous cell-seeded matrices or acellular matrices can be used as natural materials.[9]

Cells

Several types of epithelial tissues, such as bladder, oral mucosa, and skin, have been harvested from patients to obtain cells for TE

urethroplasty. Bladder mucosal tissue consists of transitional epithelial cells, also called urothelial cells, and is considered a favorable source of cells for the repair of urethral defects with the TE technique. The cells can be seeded onto a scaffold as a monoculture or co-culture with other cell types. In monoculture, the epithelial cells are used only on the luminal surface of the scaffold. However, in the more complex co-culture, in addition to the luminal epithelial cells, the opposite surface of the scaffold is seeded with fibroblasts or smooth muscle cells.[21-26]

Methods

A literature search for original articles published in English was performed in February 2022 using a PubMed database search for articles published in the past 3 decades using the keywords "urethral stricture," "tissue engineering," "regenerative medicine," "urethral disease," "stem cells," and "clinical studies." The authors reviewed the selected articles, and their findings/conclusions were incorporated into this manuscript. Only clinical studies were selected that used TE grafts for urethroplasty. Based on these criteria, a total of 18 articles were identified that were published between 1998 and 2022 and categorized into either decellularized matrices or cellularized matrices (monoculture and co-culture). All articles were reviewed according to the functional and anatomical outcomes, including complications.

Results

Decellularized Matrices

Table 1 summarizes the articles related to decellularized matrices according to the study selection process. Several articles have been published to discuss the feasibility of applying alternative grafts for urethroplasty since Atala et al[27] published a pilot study that used an acellular collagen matrix as a graft for urethroplasty in 4 patients who underwent failed hypospadias surgery. The authors used cadaver bladder submucosal tissue to obtain an inert acellular collagen matrix as a potential graft substitute. Three of the 4 patients had normal urethral caliber after 22 months of follow-up; the remaining patient developed a fistula, but the fistula was repaired successfully with the standard technique. The range of size of the neo-urethra was 5-15 cm, and the biopsies showed a stratified urethral epithelium at the surgical site.

Three years later, the same authors published another study to demonstrate the efficacy of inert acellular collagen matrix as a potential graft substitute for bulbar/penile US with a larger sample of patients (n = 28) and longer follow-up (mean = 37 months).[14] They reported that the mean success rate was 85.7% (24/28); only 4 patients developed stricture at the anastomotic site during follow-up. However, they were treated with a single-session internal urethrotomy without further intervention. In addition, 1 patient had a fistula, but it resolved spontaneously. No patients who had bulbar US showed any recurrence or complications.

Finally, 1 study compared buccal mucosa as a gold standard graft and acellular bladder matrix (ABM) for USs.[13] In total, 30 patients were randomized into 2 groups for either buccal mucosa or ABM urethroplasty. The success rates of the patients who underwent buccal mucosa graft and ABM were 100% and 66.6%, respectively. However, the success rate in patients who had a healthy urethral bed in the ABM urethroplasty group increased to 89.7%. The authors reported that ABM urethroplasty would be a reliable option for urethral repair in patients with a healthy urethral bed.

The SIS is the mid-layer of the porcine intestine obtained after mechanically removing the intestine's tunica mucosa and tunica muscularis. Many animal studies have investigated the effect of SIS on the urethral reconstruction model.[28,29] The first human study that used SIS as a graft was published in 2003, including only 1 patient with long US. The outcomes of urine flow rate and patients reported showed no recurrence during 16 months of follow-up.[30] Donkov et al[31] reported an 89% success rate in 9 patients with 4-6 cm long bulbar USs when using SIS. One patient had a recurrence, and 6 patients had post-micturition dribbling. In contrast, Hauser et al[32] reported poor outcomes in 4 of 5 patients who underwent dorsal onlay SIS grafting urethroplasty. The authors indicated that they had discontinued using SIS as a graft because of frequent complications, such as urethritis, infection, and extravasation.

The outcome of the largest case series conducted by Fiala et al.[33] which included 50 patients who underwent SIS grafting urethroplasty, reported an 80% success rate within 31.2 months (range: 24-36 months) of follow-up. While 9 of 10 patients who developed restricture had penile (4) or penobulbar (5) US, only 1 patient with bulbar stricture had a recurrence, and all recurrences occurred within 6 months postoperative. No complications were reported.

Palminteri et al[17] conducted 2 studies that reported the outcomes of SIS grafting urethroplasty. The first study included 20 patients with US who showed an 85% success rate with 21 months of follow-up. The second included 25 patients with bulbar US who showed a 76% success rate with 71 months of follow-up.[18] In 2013, Xu et al[15] reported their series outcomes when using SIS in 28 patients with 3.5-7 cm long anterior USs. Their success rate was reported as 93%, with a mean follow-up of 24.8 months.[15]

Le Roux[16] described endoscopic SIS after DVIU as a different surgical technique called endoscopic urethroplasty. The study included 9 patients with bulbar US, and only 2 of the 9 patients had normal urethral patency after endoscopic SIS placement with a 1-year follow-up. However, a few years later, the same surgical technique was applied to 10 patients with short bulbar US. The success rate was reported as 80% without complications.[34]

Small intestinal submucosa was used as a graft in another study conducted by Orabi et al.[35] which included 12 patients with hypospadias. Out of the 12, 6 patients were successfully treated with SIS graft without any intervention and good cosmetic appearance. Three of the remaining 6 patients developed fistulae, but they were repaired with the standard approach. However, the last 3 patients developed graft infections and recurrences with a mean of 23 months of follow-up.

Cellularized (Monoculture and Co-Culture) Matrices

Table 2 summarizes the studies that used cellularized (monoculture and co-culture) matrices as a graft for urethral reconstruction. A study conducted by Fossum et al[36] described the use of autologous urothelial cells seeded on the acellular dermis for the urethroplasty in 6 patients with severe hypospadias. Autologous urothelial cells were obtained from the bladder and washed before placing them onto the acellular dermis. The patients' age and follow-up

Table 1. Study Characteristics of All 12 Clinical Studies That Used Decellularized Matrices As a Graft for Urethral Reconstruction

	No of Patients	Age (Years)	Location	Etiology	Length of Stricture	Follow-Up (Months)	Biomaterial	Cells	Technique	Success rate (%)	Complications
[27]	4	4-20	Penile	Hypospadias	5-15 cm	22	ABM	No	Patch	75	Urethrocutaneous fistula: 1
[14]	28	22-61 (Mean: 40.4)	Penile: 3; bulbar: 11; peno-bulbar: 14	Trauma: 16; idiopathic: 8; infection: 4	1.5-16 cm	39	ABM	No	Patch	Penile: 66.6; bulbar: 100; peno-bulbar: 78.5	Urethrocutaneous fistula: 1
[13]	30	21-59 (Mean: 36.2)	Penile: 7; bulbar: 11; peno-bulbar: 12	Trauma: 9; idiopathic: 1; iatrogenic: 5; hypospadias: 2; catheterization: 8; infection: 4	2-18 cm (Mean: 6.9)	18-36	ABM	No	Patch	Buccal mucosa: 100%; BAM: 66.6%	NA
[31]	9	26-45 (Mean: 35.5)	Bulbar urethra	Urethritis: 5; trauma: 4	4-6 cm	18	SIS	No	Patch	89	Post-micturition dribbling: 6; lack of morning erection: 7
[32]	5	68 (Median)	Bulbar: 2; penile-bulbar: 3	Urethral trauma/instrumentation	9 cm (3.5-10)	12.4 (range: 3.7-17.5)	SIS	No	Patch	25	Urethritis: 1; infection: 1; extravasation: 1; compartment syndrome: 1
[33]	50	45-73	Bulbar: 10; bulbopenile: 31; distal penile: 9	İatrogenic: 33; inflammatory: 11; idiopathic: 4; trauma: 2	5.2 cm (4-14)	24-6	SIS	No	Patch	80	No
[18]	20	41 (Mean)	Penile: 1; bulbar: 16; penile-bulbar: 3	Unknown: 9; iatrogenic: 5; ischemic: 4; failed hypospadias: 1; traumatic: 1	3 cm (mean)	21 (range: 13-35)	SIS	No	Patch	76	No
[17]	25	40.5 (Mean)	Bulbar urethra	Unknown: 16; iatrogenic: 8; traumatic: 1	1.5-6 cm (mean: 3.3)	71 (range: 52-100)	SIS	No	Patch	85	No
[15]	28	39 (Mean)	Bulbar: 8; bulbopenile: 9; distal penile: 10; failed hypospadias: 1	Unknown: 2; urethritis: 4; iatrogenic: 10; failed hypospadias: 1; trauma: 11	3.5-7.0 cm (mean: 4.6))	24.8 (range: 12-30)	SIS	No	Patch	93	No
[16]	9	15-54	Membranous: 2; bulbar: 7	Recent pelvic fracture: 2; post-inflammatory: 7	1-4 cm	24	SIS	No	Patch	20	No
[34]	10	35.7 Mean (20-52)	Bulbar urethra	Post-inflammatory	0.5-2 cm	18-24	SIS	No	Patch	80	No
[35]	12	8 (Mean) (1.5-15)	Penile	Hypospadias	-	23 (6-36)	SIS	No	Patch	75	Graft infection: 3; fistula: 3 (repaired successfully)

ABM, acellular bladder matrix; ADM, acellular bladder matrix; PGA, polyglycolic acid; SIS, small intestinal submucosa.

Table 2. Study Characteristics of All 6 Clinical Studies That Used Cellularized (Monoculture and Co-culture) Matrices As a Graft for Urethral Reconstruction

	No of Patients	Age (Years)	Location	Etiology	Length of Stricture	Follow-up (Months)	Biomaterial	Cells	Technique	Success Rate (%)	Complications
[36]	6	14-44 months	Penile	Severe hypospadias	NR	35-69	ADM	Autologous urothelial cells	Patch	100	Recurrence: 2 (treated with successfully); fistula: 2 (treated with successfully)
[22]	5	NR	Bulbar: 2; penobulbar: 2; full-length: 11	Lichen sclerosis	NR	32-37 (mean: 33.6)	ADM	Buccal mucosa keratinocytes; buccal mucosa fibroblasts	Patch	0	No
[21]	5	11 (Median) (10-14)	Membranous urethra	Trauma	4-6 cm	36-76 (mean: 71)	PGA	Autologous urothelial cells; bladder smooth muscle cells	Tubularazied	100	No
[26]	99	55.9 (Mean)	Bulbar: 82; penile: 18	Iatrogenic: 36; idiopathic: 9; trauma: 5; other: 4; unknown: 45	3.8 cm	12-24	MukoCell	Buccal mucosa keratinocytes; buccal mucosa fibroblasts	Patch	67.5	No
[25]	39	57 Mean (28-81)	Bulbar: 29; penobulbar: 6; penile: 3	Idiopathic: 11; catheter: 12; instrumentation: 14; infection: 1	5 cm (Median)	55 (Median); 12-77 (range)	MukoCell	Buccal mucosa keratinocytes; buccal mucosa fibroblasts	Patch	84.6	No
[24]	77	60 (Median)	Trauma: 8; iatrogenic: 39; idiopathic: 21; lichen sclerosus: 1; hypospadias: 2; radiogenic: 4; others: 2	Bulbar: 45; penobulbar: 16; penile: 10; bulbomembranous: 4; concomitant bulbar/ penile: 2	4 cm (Median)	38 (Median)	MukoCell	Buccal mucosa keratinocytes; buccal mucosa fibroblasts	Patch	68.8	Fistula: 1

ABM, acellular bladder matrix; ADM, acellular dermal matrix; PGA, polyglycolic acid; SIS, small intestinal submucosa.

ranges were 14-44 months and 3.5-5 years, respectively. The authors reported that 2 patients developed strictures and were treated either conservatively or with internal urethrotomy. In addition, 2 other patients had fistulae that were repaired with the standard approach. The parents of the patients were satisfied regarding the cosmetic appearance, and the biopsy of 3 patients showed urothelial cells in the mucosal lining.

The follow-up of the case series was updated 5 years later, with a median of 7.25 years (range = 6-8 years). It was reported that no patients developed strictures, and all patients maintained an excellent cosmetic appearance.[23]

The first reported clinical use of tissue-engineered oral mucosa for US was published by Bhargava et al.[22] The matrix was obtained from donor de-epidermis dermis, then cultured buccal mucosa keratinocytes and fibroblasts were placed onto the scaffold. Five patients with US secondary to lichen sclerosis underwent urethroplasty during either first- (2 patients) or second-stage (3 patients) procedure. It was necessary to remove the whole graft in 1 patient because of extensive fibrosis; another patient needed partial graft excision. The remaining 3 patients also required urethral instrumentation to be able to void. The authors reported that the study was discontinued due to its high costs, ease of harvesting buccal mucosa, and the small number of patients who needed grafts longer than 15 cm for urethral repair.[6]

Raya-Rivera et al[21] conducted a study using a PGA matrix as a scaffold in which autologous urothelial and bladder smooth muscle cells were seeded into the luminal and outer surfaces, respectively. Bioengineered tabularized grafts were implanted in 5 adolescent patients with severe membranous urethral defects secondary to trauma. During the follow-up (36-76 months), the wide caliber urethral lumen was shown in all patients through serial voiding cystourethrograms and urethroscopy. In addition, urethral biopsies from the constructed urethra showed typical urethral architecture at 3 months post surgery.

MukoCell® (UroTiss Europe GmbH, Dortmund, Germany) became the first commercially available graft produced in Germany for the treatment of US. Initially, approximately 0.5 cm^3 buccal mucosal tissue is harvested for epithelial cells. The mucosal cells from the small biopsy are cultured and then seeded on the scaffold. The construct can be prepared as a graft for implantation 3 weeks following cell culture.[37] Three clinical studies, described later, have reported the effectiveness of the MukoCell in patients with US.[24-26]

A multicenter prospective study was conducted in 8 different hospitals in Germany, which included 99 patients with USs (bulbar: 82%; penile: 18%). MukoCell was used as a graft for all patients who underwent substitution urethroplasty. The overall success rate at 12 months was 67% (0%-85%); however, the success rate was lowest in 2 low-volume centers (0% and 50%). The authors reported that TE oral mucosal graft was a safe and effective option compared to buccal mucosa with a high volume of surgeons.[26]

Barbagli et al[25] conducted a study to define surgical techniques and outcomes of MukoCell in 38 patients with USs in different locations (29 bulbar, 6 penobulbar, and 3 penile USs). According to stricture length and location, 4 different techniques, including ventral onlay, dorsal onlay, dorsal inlay, and combined, were performed. Only 6 patients developed stricture during a median of 55 months (range: 12-77) of follow-up, and there were no differences among the techniques in terms of success rate.

The last study investigated the safety and efficacy results of MukoCell in 77 patients who underwent anterior urethroplasty in a single center. The overall success rate was 69%, with a median of 38 months of follow-up. Interestingly, the success rate increased to 100% in patients who had no previous intervention but decreased to 31% in patients who had more than 10 interventions. The virgin case might be the best candidate for using a TE oral mucosa graft.[24]

Discussion

Tissue engineering grafting is a safe and promising field of regenerative medicine for patients with USs. Although several case series and preclinical studies have been published in the last 2 decades, using TE grafts is still not widely used and remains controversial.[10] Several reasons have been asserted for the limited use of TE grafts for urethral substitution.

First, given the excellent results of buccal mucosa urethroplasty, there are doubts about the necessity of alternative grafts. The buccal mucosa has been one of the most-used grafts to substitute for urethroplasty since Sapezhko first described using oral mucosa for urethroplasty in 1894.[38] Currently, the literature reports that the success rate of free graft urethroplasty is 88%, with 40 months of follow-up.[3,4] In addition, the buccal mucosa can be used for both penile and bulbar USs with minimal complications and low donor site morbidity.[39]

Despite the excellent results of the buccal mucosa, in the case of extensive US, the buccal mucosa might be insufficient because of its limited size. Also, harvesting long buccal mucosa grafts increases the operation duration, which may cause intraoperative complications such as compartment syndrome and donor site morbidity. An alternative graft might be needed for patients with recurrent US after failed buccal mucosa urethroplasty. Tissue engineering grafts may resolve these challenges.[40]

Cost is another challenge related to developing TE grafts. The existing autologous grafts are undoubtedly more cost-effective than TE grafts because advanced biotechnological facilities, laboratories, and highly specialized personnel are required for creating new products.[41] In addition, the development of cell-seeded constructs is a time-consuming process. However, this challenge may be eliminated with scientific and technological improvements.[42]

The outcomes of clinical studies on TE grafts remain inconclusive because of the inadequate quality of existing trials. Numerous variables can affect the outcome of reconstructive urethral surgery, including etiology, length and location of the stricture, preoperative intervention, and surgical experience. However, the cohort of studies included in this article is rather heterogeneous, and the sample sizes are relatively small. In addition, only 1 randomized controlled study was published to investigate the efficacy of TE grafts compared to the buccal mucosa.[13]

In this article, we reviewed the outcomes of the current literature in terms of using TE grafts for urethral substitution. While the studies that used acellular grafts were mainly carried out in the early 2000s, cellular TE grafting has recently gained popularity. Most clinical studies have used decellularized grafts because researchers have greater experience using decellularized materials in the other specializations of TE, such as skin grafting.

Small intestinal submucosa is one of the most used TE grafts for urethral substitution. Nine studies were reviewed in this article, with varied success rates between 25% and 93%. The number of patients included in these studies was relatively low, and there are no randomized controlled studies to compare SIS with buccal mucosa grafting. While immunological reactions were not seen in any studies, graft infection was reported in 2 studies.[32,35]

Acellular bladder matrix is a single TE graft that was compared to buccal mucosa in a randomized controlled study. In total, 30 patients with complex anterior USs were randomized into 2 groups for either buccal mucosa or ABM urethroplasty. The authors reported that the success of the ABM in patients with healthy urethral beds was comparable with buccal mucosa urethroplasty (89.9% and 100%, respectively).[13]

Most patients who received a TE graft had complex USs, such as full-length stricture, failed urethroplasty, or lichen sclerosis. It is well known that the success rate of complex US is quite a bit lower than in the index cases.[43] A study showed that complication-free and functionality success rates in patients who underwent complex 2-stage urethroplasty were 62% and 67%, respectively.[43] The results of current studies that used TE grafts are not inferior to current treatment options, mainly in patients with complex USs. In this vein, a systematic review meta-analysis was carried out to assess the outcomes of using TE grafts for substitution urethroplasty. The authors reported that the results of using TE grafts were comparable to current treatment options, and TE grafting was a potential option for urethroplasty.[10]

The scaffold of cellular TE grafts can be produced as either tubularized or patch. In the tubularized approach, 2 different cells are seeded in both the inner and outer surfaces of the scaffold.[44,45] Only 1 study that used a tubularized PGA matrix as a construct has been published in the literature; it showed a 100% success rate in 5 patients who had membranous defects.[21]

The first cellular patch product, MukoCell, was recently approved for urethral substitution in Germany.[37] Three case series using MukoCell as a graft have been published and showed 67.5%, 68.8%, and 84.6% success rates, respectively. However, the patients included in these studies were quite heterogeneous, and the sample sizes were relatively small. Also, no randomized controlled studies have been published to evaluate the efficacy of MukoCell in urethroplasty (Table 2).

Taking biopsies from the buccal mucosa or bladder presents the potential for morbidity for the creation of autologous cellularized constructs. However, Fossum et al[23] managed to obtain autologous urothelial cells via the bladder; they washed and then placed them onto the acellular dermis successfully. Hence, a tissue biopsy may not be a necessity for future studies.[36,46]

Overall, it appears that scaffolding with cells has promising results for the future. In particular, tubularized scaffolds constructed from co-cultured cells might be the more appropriate direction for TE urethroplasty.

Conclusion

Tissue engineering grafts are a promising technique in the field of urethral reconstruction. As the current data do not recommend the approach in routine clinical practice, TE grafts might be an option for specific, select patients. High-quality evidence through randomized controlled studies with larger sample sizes is required to determine accurate outcomes with long follow-up.

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