Anterior Urethroplasty Using a New Tissue Engineered Oral Mucosa Graft: Surgical Techniques and Outcomes

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Abbreviations and Acronyms

GMP = good manufacturing practice

LS = lichen sclerosus

Qmax = maximum urinary flow

RUG = retrograde urethrogram

TEOMG = tissue engineered oral mucosal graft

VCUG = voiding cystourethrogram

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Purpose: We investigated whether tissue engineered material may be adopted using standard techniques for anterior urethroplasty.

Materials and Methods: We performed a retrospective multicenter study in patients with recurrent strictures, excluding those with failed hypospadias, lichen sclerosus, traumatic and posterior strictures. A 0.5 cm^2 oral mucosa biopsy was taken from the patient cheek and sent to the laboratory to manufacture the graft. After 3 weeks the tissue engineered oral mucosal MukoCell® graft was sent to the hospital for urethroplasty. Four techniques were used, including ventral onlay, dorsal onlay, dorsal inlay and a combined technique. Cystourethrography was performed 1 month postoperatively. Patients underwent clinical evaluation, uroflowmetry and post-void residual urine measurement every 6 months. When the patient showed obstructive symptoms, defined as maximum urine flow less than 12 ml per second, the urethrography was repeated. Patients who underwent further treatment for recurrent stricture were classified as having treatment failure.

Results: Of the 38 patients with a median age of 57 years who were included in study the strictures were penile in 3 (7.9%), bulbar in 29 (76.3%) and penobulbar in 6 (15.8%). Median stricture length was 5 cm and median followup was 55 months. Treatment succeeded in 32 of the 38 patients (84.2%) and failed in 15.8%. Success was achieved in 85.7% of ventral onlay, 83.3% of dorsal onlay, 80% of dorsal inlay and 100% of combined technique cases. No local or systemic adverse reactions due to the engineered material were noted.

Conclusions: Our findings show that a tissue engineered oral mucosa graft can be implanted using the same techniques suggested for anterior urethroplasty and native oral mucosa, and guaranteeing a similar success rate.

Key Words: urethral stricture; mouth mucosa; tissue engineering; outcome and process assessment (health care); urologic surgical procedures, male

For many years stem cell therapy was limited to bone marrow transplantation for hematological diseases and epidermis transplantation for burns but the last 10 years have seen an exponential growth in experimental regenerative medicine entering the clinical arena.[1] Results vary from unequivocal clinical efficacy for previously incurable diseases to more

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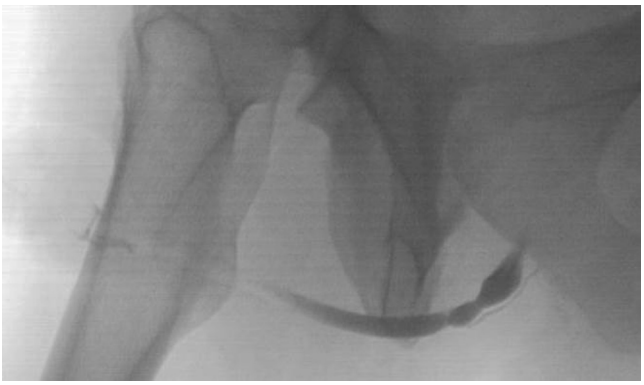

Figure 1. Preoperative RUG shows recurrent bulbar urethral stricture after urethrotomy.

frequently a modest or null effect and the reasons for these widely different outcomes are starting to emerge.[1]

Despite the increasing number of publications referring to tissue engineering procedures and technical success in the laboratory and in experimental animals, clinical application in patients has been modest and inconclusive.[1,2] The gap between investigative in vitro studies and clinical application of tissue engineered materials in patients is also clearly evident for urethral reconstruction.[2] Currently in the literature only 7 reports of clinical application of different tissue engineered materials for different urethral reconstruction are available with a total of 140 patients.[3–9]

The first anterior urethroplasty using a tissue engineered material was reported in 1990 by Romagnoli et al, who treated 2 children who had penoscrotal hypospadias with cultured epithelial cells.[3] In 1993 the same investigators described a new tissue engineered technique for 1-stage hypospadias repair in 8 young patients.[3,4] In 2008 Bhargava et al reported placing an autologous tissue engineered oral mucosa in 5 patients with anterior LS strictures.[5] In 2001 Raya-Rivera et al reported placing a tissue engineered autologous tubular urethra in 5 boys with long, complex, traumatic posterior urethral strictures.[6] More recently preliminary data on the efficacy of a new TEOMG were reported in an increasing number of patients.[7–9]

We describe the technical procedures and the clinical outcomes of urethroplasty using TEOMG. We tested the hypothesis that TEOMG can be adopted using the same standard 1-stage urethroplasty techniques as for native oral mucosa, guaranteeing a similar clinical outcome.

MATERIALS AND METHODS

We performed a retrospective multicenter study of prospectively collected data on a cohort of patients who underwent TEOMG urethroplasty between 2010 and 2016 in Germany. Patients were requested to read and sign the informed consent explaining the surgical procedure and the complications. Study inclusion criteria were penile, bulbar and penobulbar urethral strictures. Exclusion criteria were LS, failed hypospadias repair, and traumatic and posterior strictures. The primary outcome of the study was to evaluate the overall results of urethroplasty (success vs failure) using 4 standard techniques. The secondary outcome was to evaluate the outcome according to any surgical technique. The MukoCell TEOMG implanted in the context of this study has market authorization in Germany.

Preoperative Patient Investigations

Before urethroplasty information was gathered on demographic and medical history. Preoperatively physical

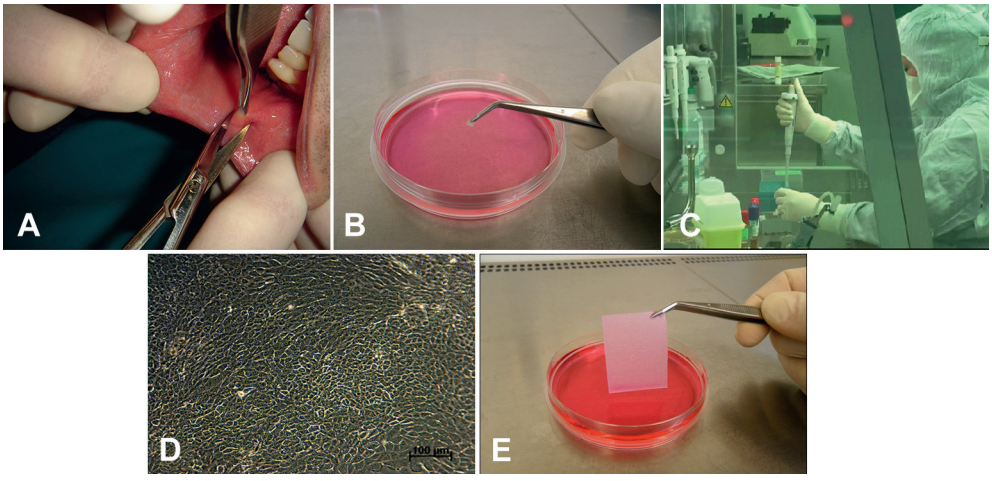

Figure 2. *A* and *B*, thin oral mucosa biopsy is taken from patient cheek. *C*, biopsy is sent to GMP laboratory to manufacture graft. *D*, microscopy shows human cultured oral mucosa cells with specific phenotype. Scale bar indicates 100 µ. *E*, cell membrane construct is ready for implantation after 3 weeks of culture. Product is sterile and quality is standardized.

examination results, vital sign measurements, electrocardiogram, serological examinations and concomitant medication were collected. All patients underwent a complete preoperative urological examination including uroflowmetry, post-void residual urine measurement, VCUG, urethroscopy and RUG (fig. 1).

Tissue Engineered Oral Mucosal Graft

Manufacturing. With the patient under local anesthesia a thin 0.5 cm^2 oral mucosa biopsy was taken from the cheek and sent to the GMP laboratory, which was the graft manufacturing site (fig. 2, *A* to *C*). Mucosal cells from the tiny biopsy were cultivated. After reaching confluence they were seeded on a biodegradable membrane (fig. 2, *D*). The cell-membrane construct was ready for implantation after 3 weeks of culture (fig. 2, *E*). The 2.8 × 3.8 cm product was sterile and as an industrial product its quality was standardized. After implantation the membrane degraded within a few weeks and was replaced by new regenerated mucosa tissue.

The TEOMG was produced according to GMP principles according to European Union legislation in a laboratory certified by competent authorities. We previously fully reported our laboratory and experimental animal studies to assess TEOMG safety, pharmacology, pharmacokinetic, toxicology and tumorigenicity.[7,8]

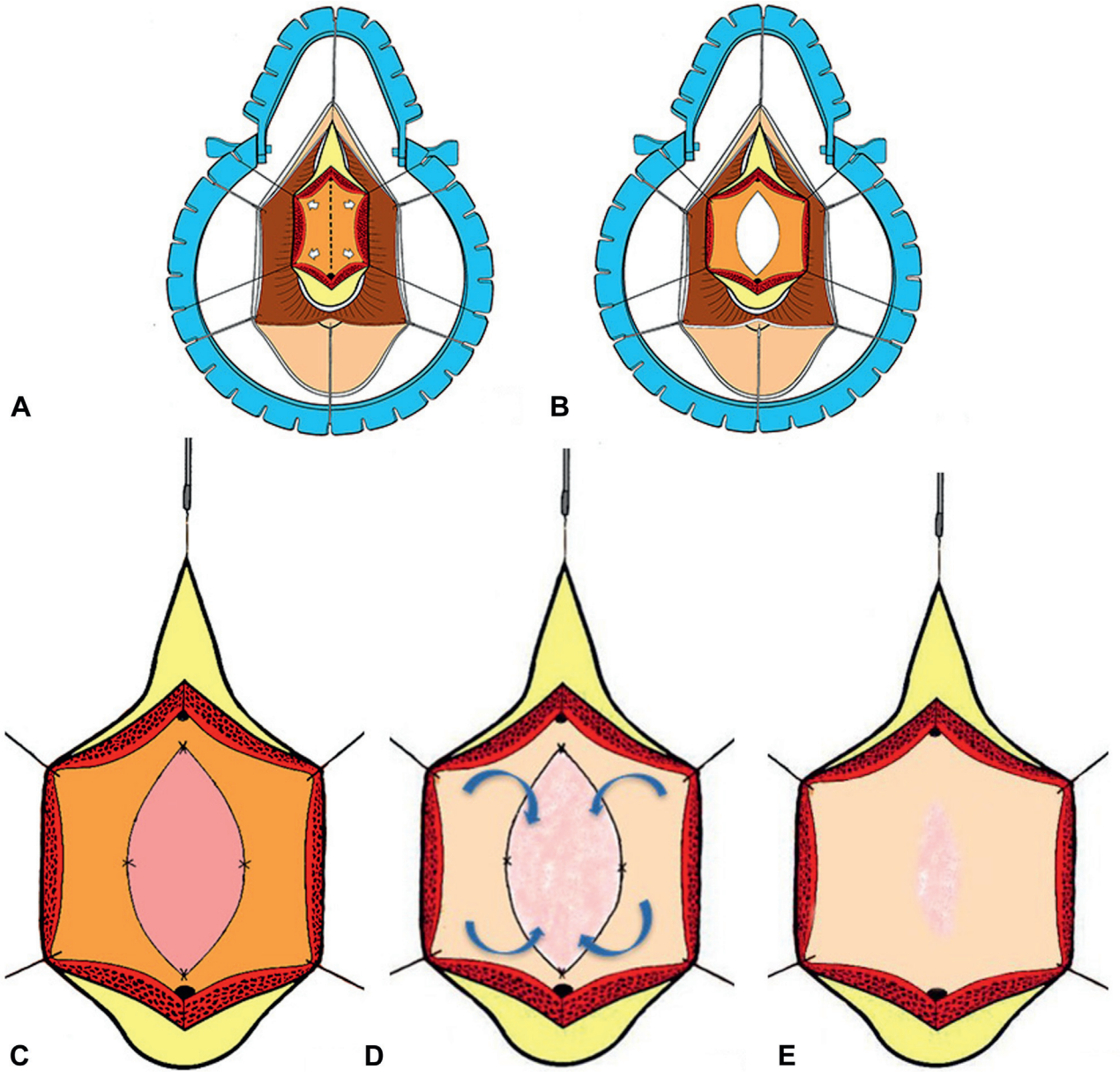

Figure 3. *A*, urethral plate is longitudinally incised. *B*, wide window is created, leaving 2 strips of original urethral mucosa intact. *C*, TEOMG is fixed to urethral mucosal plate. *D* and *E*, 2 strips of original urethral mucosa stimulate urethral regeneration, enclosing TEOMG in process.

Urethroplasty. The TEOMG was implanted in the urethra using 4 techniques according to surgeon preference. The ventral onlay graft procedure was first described in 1996 by Wessells and McAninch,[10] and Morey and McAninch.[11,12] In 2011 and 2013 Barbagli et al provided a clear step-by-step description of this technique.[13,14] The dorsal onlay graft procedure was first described in 1996 by Barbagli et al.[15,16] Barbagli et al also reported a clear step-by-step description of this technique in 2012.[17]

The dorsal inlay graft procedure was first suggested for hypospadias repair in 1999 by Hayes and Malone.[18] In 2001 Asopa et al suggested applying this technique to anterior urethroplasty.[19] A clear step-by-step description of this technique for penile urethroplasty was described by Barbagli et al in 2016.[20] The ventral urethral surface is longitudinally opened to expose the stricture tract. The mucosal urethral plate is longitudinally incised, extending the incision in the healthy urethral mucosa distal and proximal to the narrow tract (fig. 3, *A*). The longitudinal incision is transformed into a wide window, leaving 2 strips of original urethral mucosa intact (fig. 3, *B*). The TEOMG is gently transferred into the operating field (fig. 4, *A*). The TEOMG is gently inserted in the urethral plate window and fixed to urethral mucosa with a few 5-zero polyglactin stitches (fig. 4, *B* to *D*). A grooved silicone 16Fr Foley catheter is inserted (fig. 4, *E*). The urethra is closed in a single layer. The combined procedure combines the ventral graft with the Asopa graft inlay.[19]

These techniques were used in a standard way as fully reported and described in the literature[10–20] without any significant surgical changes. After any procedure the 16Fr Foley catheter remained in place for 1 month, and RUG and VCUG were performed (fig. 5).

Followup Criteria

Patients underwent clinical evaluation, uroflowmetry and post-void residual urine measurement every 3 months during year 1 and every 6 months during year 2. RUG and VCUG were repeated when the patient showed recurrent urinary tract infection, obstructive symptoms or Qmax less than 12 ml per second. Patients who underwent any further treatment for recurrent stricture were classified with treatment failure.

RESULTS

A total of 38 patients were enrolled in the study. Median age was 57 years (range 28 to 81), including 28 to 49 in 11 patients (29%), 50 to 69 years in 16 (42%) and 70 years or greater in 11 (29%). Table 1 summarizes stricture clinical characteristics, including site, etiology, length and previous surgical treatments. Median preoperative Qmax was 5.9 ml per second (range 3.5 to 8.9). The technique was ventral onlay in 21 cases (55.3%), including 15 bulbar and 6 penobulbar cases, dorsal onlay in 6 (15.8%), including 3 bulbar and 3 penile cases, dorsal inlay in 10 bulbar cases (26.3%) and the combined technique in 1 bulbar case (2.6%).

Median followup was 55 months (range 12 to 77). Of the 38 cases 32 (84.2%) were classified as

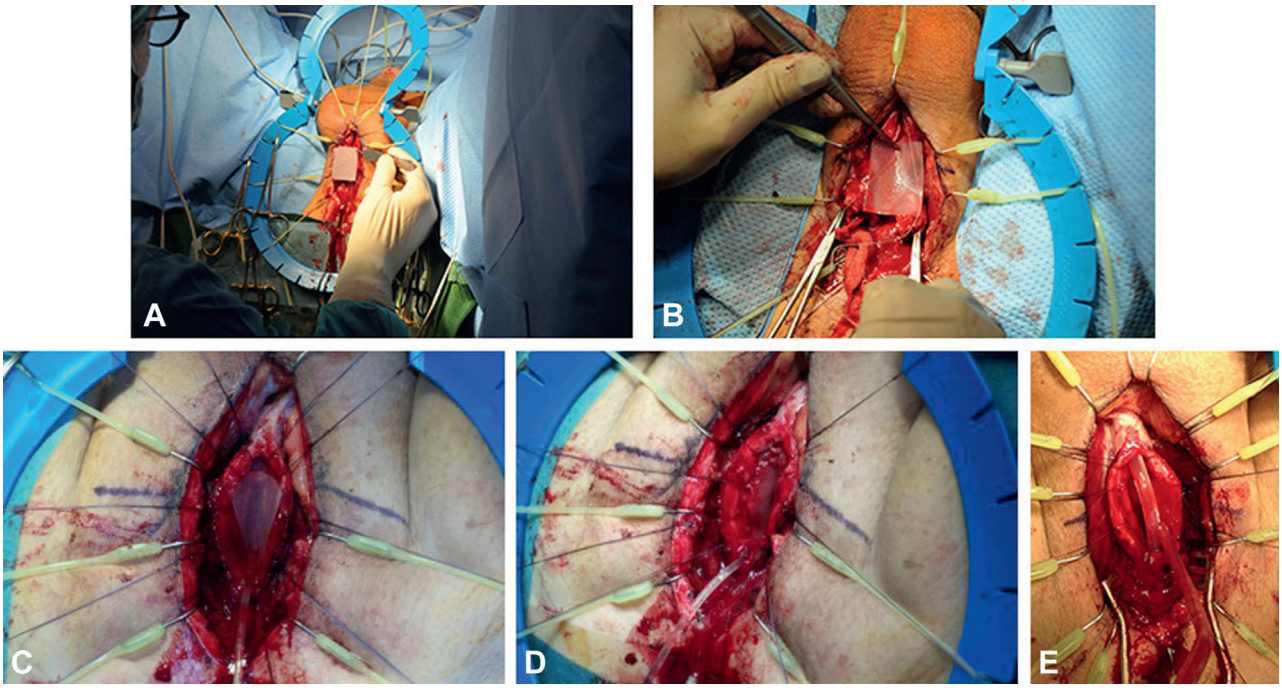

Figure 4. *A*, TEOMG graft is transferred into operating field for transplantation. *B* to *D*, TEOMG is inserted in urethral plate window and fixed to urethral mucosa. *E*, silicone grooved 16Fr Foley catheter is inserted.

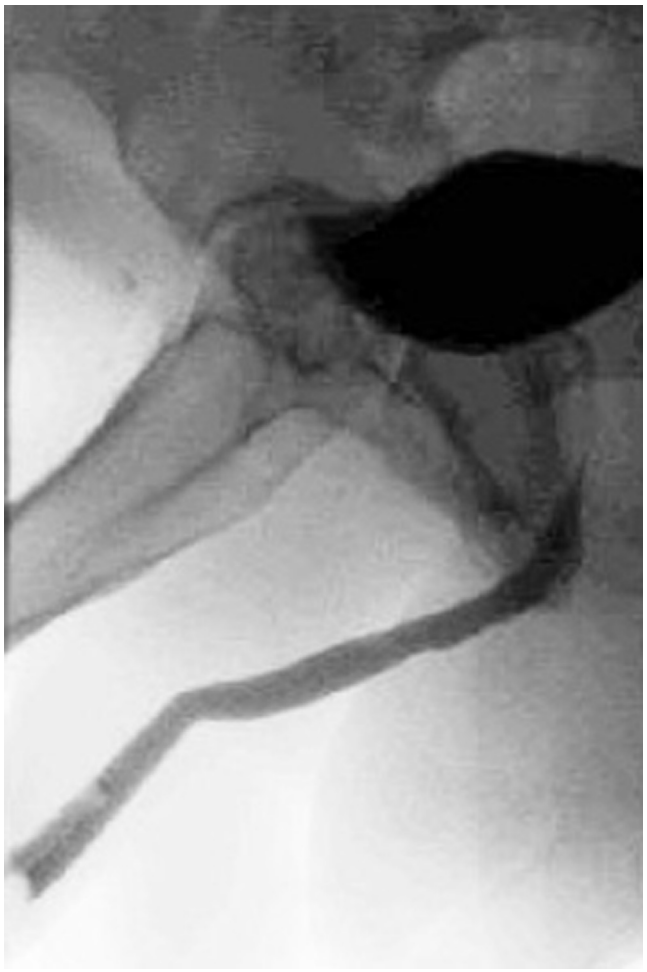

Figure 5. Postoperative RUG reveals normal canalization of reconstructed bulbar urethra.

successes and 6 (15.8%) were classified as failures. Success and failure were stratified by stricture clinical characteristics (table 1). Due to the small sample size no statistical comparative analysis was done. Median postoperative Qmax was 20.6 ml per second (range 12.4 to 48.3).

The success rate was 85.7% for ventral onlay, 83.3% for dorsal onlay, 80% for dorsal inlay and 100% for the combined technique. According to stricture site the overall success rate was 66.7% for penile, 93.1% for bulbar and 50% for penobulbar urethroplasty. The ventral onlay technique was 100% successful when used in the 15 bulbar urethra cases and 50% successful when used at the penobulbar site in 6 cases. The dorsal onlay was 100% successful when used in the 5 bulbar urethra cases and 0% successful when used in the single penile urethra case. The dorsal inlay, which was applied only in the bulbar urethra, had an 80% success rate. Table 1 summarizes success rates according to patient and stricture features.

Table 1. *Long-term success rate of urethroplasty with tissue engineered oral mucosal graft according to patient and stricture features*

	No. Pts (%)	No. Success (%)	No. Failure (%)
Overall	38 (100)	32 (84.2)	6 (15.8)
Age:			
28–49	11	9 (81.8)	2 (18.2)
50–69	16	14 (87.5)	2 (12.5)
70 or Greater	11	9 (81.8)	2 (18.2)
Stricture site:			
Penile	3 (7.9)	2 (66.7)	1 (33.3)
Bulbar	29 (76.3)	27 (93.1)	2 (6.9)
Penobulbar	6 (15.8)	3 (50)	3 (50)
Stricture etiology:			
Idiopathic	11 (29)	10 (90.9)	1 (9.1)
Catheterization	12 (31.6)	9 (75)	3 (25)
Instrumentation	14 (36.8)	12 (85.7)	2 (14.3)
Infection	1 (2.6)	1 (100)	—
Stricture length (cm):			
1–2	1 (2.6)	1 (100)	—
2.1–3	3 (7.9)	3 (100)	—
3.1–4	8 (21)	7 (87.5)	1 (12.5)
4.1–5	6 (15.7)	4 (66.7)	2 (33.3)
5.1–6	6 (15.7)	5 (83.4)	1 (16.6)
6.1–7	4 (10.5)	3 (75)	1 (25)
7.1 or Greater	10 (26.3)	9 (90)	1 (10)
Previous urethrotomy or urethroplasty:			
None	2 (5.3)	2 (100)	—
1	6 (15.8)	6 (100)	—
2	9 (23.7)	8 (88.9)	1 (11.1)
3	4 (10.5)	3 (75)	1 (25)
4	7 (18.4)	5 (71.4)	2 (28.6)
5 or Greater	8 (21)	6 (75)	2 (25)
Missed	2 (5.3)	2 (100)	—

The stricture recurred in 2 patients (33.3%) after 3 months, in 1 (16.7%) after 6 months, in 1 (16.7%) after 10 months and in 2 (33.3%) after 12 months. The site of stricture recurrence was a distal anastomotic ring in 2 cases (33.3%), a proximal anastomotic ring in 3 (50%) and the whole grafted area in 1 (16.7%). Failure was treated with a permanent urethral catheter in 1 patient (16.7%), dilations in 2 (33.3%), urethrotomy in 1 (16.7%) and urethroplasty with native oral mucosa in 2 (33.3%). The patient who underwent urethrotomy experienced a new recurrence later, which was successfully treated with urethroplasty using native oral mucosa. The 2 cases of urethroplasty with native oral mucosa were successful. No local (oral-urethral) or general adverse events related to TEOMG were observed.

DISCUSSION

Our findings show that TEOMG urethral reconstruction is feasible with a success rate similar to that of current 1-stage urethroplasty with oral mucosa graft regardless of the technique that we used.

Native oral mucosa is known to be an appropriate tissue for urethral reconstruction. Like any other

native tissue, excision is cost-effective but not always free of complications (table 2). Therefore, efforts have been made for many years to develop a new graft for urethroplasty which avoids excising oral mucosa.

MukoCell is an autologous, tissue engineered graft for urethroplasty which can be produced from a tiny biopsy from the mouth of the patient. To our knowledge our work represents a significant message in the field of urethral stricture repair using a tissue engineered material. TEOMGs placed by the standard techniques that are basically suggested for anterior urethroplasty provided a high success rate at the 5-year median followup. Success rates are similar to those of native oral mucosa grafts, which have a high 93.1% success rate in the bulbar urethra and lower rates of 66.7% in the penile tract and 50% for penobulbar strictures. The stricture site represents a negative prognostic factor for the ventral and dorsal onlay procedures. No local (oral) or systemic adverse reactions related to the TEOMG implant were recorded. The TEOMG avoided any complications or sequelae in the mouth after graft harvesting.

Recently a study on comparative assessment of cultures from oral and urethral stem cells for urethral regeneration showed that, although few differences appeared in oral vs urethral mucosa, they can be equally useful for tissue engineering of the urethral tract.[21] The comparison of all parameters highlighted a similarity of 2 epithelia except for a higher migration capacity of oral mucosa colonies, which suggested better wound healing potential of oral vs urethral epithelium. Additionally, the harvesting biopsy site of oral mucosa is simpler and less invasive than urethral mucosa biopsy.

We emphasize the limits of our study. This TEOMG is authorized for the market only in Germany. To be fully used in the other European countries this product must be authorized by the EMA (European Medical Agency) and in the best case scenario reimbursed by the public health care system. On the other hand, harvesting buccal mucosa is a cost-effective technique but it requires an additional operation which is associated with potential complications (table 2).[22–28] Currently the price of each MukoCell graft is €4,630 in Germany.

Nevertheless, the aim of our study was not the economic aspects of the success of tissue engineered products in clinical practice or the ethical aspects of the question of how much it is worth to avoid native tissue excision and its potential associated complications. In this report we present the initial results of different surgical techniques in the treatment of urethral strictures in the long term using a new technology which is available as a standardized industrial product.

Table 2. *Reported short-term and/or long-term complications at oral site after harvesting oral mucosa segments for urethroplasty in select literature*

References (complications)	% Complications
Zhang et al:[22]	
Postop pain	100
Perioral numbness 7 days postop	23
Complications 6 mos postop	41
Complications 12 mos postop	20
Lumen et al:[23]	
Eating + drinking 3 days postop	24–62
Speaking 3 days postop	55–93
Speaking 14 days postop	14–55
Dysgeusia 3 days postop	14–48
Eating 14 days postop	45
Oral tightness 14 days postop	7–41
Sensitivity disorders, eg due to scar formation, 6 mos	31–45
Barbagli et al:[24]	
More than slight pain	Greater than 14
Late patient dissatisfaction	10
Difficulty opening mouth	5
Dry mouth	4
Problems smiling	2
Fasolis et al[25] (long-term complications)	22
Jang et al:[26]	
Persistent oral contractures	20
Persistent pain	19
Persistent salivary flow changes	10
Persistent neurosensory deficits	40
Wood et al:[27]	
Postop pain	83
Postop pain worse than expected	51
Perioral numbness	68
Residual numbness	26
Difficulty opening mouth	67
Persistent difficulty opening mouth	9
Salivation changes	11
Dublin + Stewart:[28]	
Persistent numbness	16
Persistent oral tightness	32

Moreover, the sample size of our patient series was small and, thus, the results may not be fully sufficient to draw definitive conclusions. No multivariable analysis was performed to predict success or failure. This prospective but retrospectively evaluated study had no control group. Furthermore, the absence of quality of life questionnaires or patient reported outcome measures is another limitation. That is particularly true when we investigated the outcome of anterior urethral reconstruction with oral mucosa graft, which involves not only functional but also aesthetic and sexual domains.

Before applying MukoCell in our patients the safety, pharmacology, pharmacokinetics, toxicology and tumorigenicity of the TEOMG was fully assessed in vitro and in experimental animal studies.[7,8] The clinical safety and efficacy of the product have additionally been investigated in a prospective observational study.[9] The use of any tissue engineered material in humans also requires

2 important issues, which are proper selection of patient candidates for these procedures and adequate surgical techniques. The literature provides no evidence or support due to the lack of data on these issues.

We avoided using MukoCell in patients with LS or failed hypospadias repair and we do not yet have experience with this product for these challenging indications. Moreover, to date we have avoided using MukoCell in 2-stage techniques because this experience is also missing. The main aim of our current study was to present to the urological community the long-term results of the different surgical techniques which we selected for the implant as a standardized tissue engineered product in the anterior urethra.

The current literature on tissue engineered materials for urethral reconstruction is mainly based on laboratory and in vitro experimental issues. The question "How can I use this material?" remains mostly unanswered. In our study we covered this important issue when discussing the application of new tissue engineered materials in urethral reconstruction. Finally, we report that today we could perform safe and effective anterior urethroplasty with the new MukoCell tissue engineered material using the standard techniques of 1-stage native oral mucosa graft urethroplasty.

CONCLUSIONS

In our study we moved tissue engineering from the laboratory to the patient who required anterior urethroplasty. The results that we achieved using standard surgical techniques are satisfactory. The stricture site and previous treatments but not the single surgical technique were the factors negatively influencing the outcome.

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EDITORIAL COMMENTS

For nontraumatic and longer strictures of the anterior urethra the role of genital skin flaps has decreased slowly in the last 20 years. Flaps are now reserved for complex and post-radiation strictures.[1] Today oral mucosal grafts have gained popularity as the material of choice for augmentation in most cases.

What is the future? The technique of harvesting a tiny piece of oral mucosa, sending it to the laboratory and culturing cells in the laboratory was standardized in this study (reference 8 in article). The TEOMG was applied using 4 techniques to augment the urethral stricture during open urethral stricture repair surgery. Success rates are comparable to those of current techniques of oral mucosal graft urethroplasty.

The TEOMG is expensive and may be useful in patients with oral submucosal fibrosis. They may also be useful in those who play wind musical instruments, and professors and lawyers whose job is to speak professionally.

Sanjay Balwant Kulkarni
Center for Reconstructive Urology
Pune, India

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Anterior urethral strictures present a reconstructive challenge. Various techniques have been developed to improve the chances of long-term urethral patency, including oral mucosa grafts. Although harvesting buccal mucosa is an expedient technique which is cost-effective and done easily by reconstructive urologists, it is not a perfect solution and complications can arise.

To address these limitations the authors present their retrospective multicenter study investigating the efficacy of using tissue engineered graft material derived from a "tiny" biopsy of oral mucosa in patients with anterior urethral strictures. The study population included patients who underwent graft enhanced urethroplasty using several standard techniques. At a median followup of 55 months the reported overall success rate is 84.2%.

Although it is limited by its lack of a control group as well as the graft current cost and limited availability, this study may indicate the future direction of urethral surgery in which we are able to use graft material developed from the native patient tissue. Like many new technologies in medicine, initial costs can only be reduced once there is a clear demonstration of success and safety for the patient. This study takes the first step in that direction.

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REPLY BY AUTHORS

The comments adequately indicate the scenario. Currently many patients may require TEOMG, particularly patients who refuse mouth graft harvesting, patients with a congenitally small mouth, ie the Chinese population (reference 22 in article), patients with a small mouth opening due to

previous trauma or surgery in the mandibular arch, patients requiring large bilateral graft harvesting, which represents a significant predictor of patient dissatisfaction (reference 24 in article), patients requiring large rectangular graft harvesting for 2-stage urethroplasty and patients with recurrent urethral stricture who have already undergone graft harvesting from each cheek.

We are aware of the limitations of our work. First is the absence of a control group and second is the cost. To answer those 2 issues we plan a comparative study of native vs tissue engineered oral mucosa to demonstrate the noninferiority of our technique, considering the success rate and superiority in terms of the absence of any complications in the mouth. Finally, we do not think that cost should block the evolution of tissue engineering. Many new techniques, ie robotic surgery, have been perceived as expensive at the beginning but later use became clinically routine.