Universitat de Girona
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# BUCCAL MUCOSA GRAFT VERSUS MUKOCELL® TECHNIQUE URETHROPLASTY

## A RANDOMIZED OPEN-LABEL CLINICAL TRIAL

FINAL DEGREE PROJECT

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*M'agradaria donar les gràcies a totes les persones que han fet possible aquest treball:*

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# INDEX

# ABBREVIATION LIST

| | |
|---|---|
| **AEMPS** | Asociación Española de Medicamentos y productos sanitarios |
| **BMG** | Buccal mucosa graft |
| **BPE** | Benign prostatic enlargement |
| **BXO** | Balanitis xerotic obliterans |
| **CT** | Computed tomography |
| **DVIU** | Direct vision internal urethrotomy |
| **EMA** | European Medicine Agency |
| **EPA** | Excision and primary anastomosis |
| **GMP** | Good Manufacturing Practice |
| **HUDJT** | Hospital Universitari Doctor Josep Trueta |
| **LS** | Lichen sclerosis |
| **LUTS** | Low urinary tract symptoms |
| **MRI** | Magnetic resonance imaging |
| **PVR** | Post-void residual |
| **RUG** | Retrograde urethrogram |
| **SP** | Super pubic |
| **TEMB** | Tissue-engineered buccal mucosa |
| **TURNBC** | Transurethral resection of bladder neck contracture |
| **UTI** | Urinary tract infection |
| **VCUG** | Voiding cystourethrogram |

# FIGURES AND TABLES

# ABSTRACT

## Background

Urethral strictures are common and increasingly in ageing population, especially the bulbous urethral stricture. There are multiple causes, the main ones are iatrogenic and due to inflammation. Because of this there a large number of different treatments, depending on the localization, the length or even the cause. The main treatment in bulbar urethral strictures is the use of buccal mucosa graft urethroplasty, which is one of the recent developments in urethral surgery, even thought, it still has some perks, like the oral complications underlying, and the fact that it cannot be used in extensive strictures, due to the limited extension of oral mucosa. Looking forward to the future a real gate opens with the application of tissue engineering to obtain oral mucosa, the main product now is MukoCell®. This new TEBM would diminish all the complications regarding the buccal mucosa harvest, such as are swelling and scarring, injuries to the salivary gland orifices, and problems with the intake of food and restriction of the opening of the mouth.

## Objective

The aim of this study is to register and compare the post-intervention outcomes in the different functional tests in patients undergoing the urethroplasty using the MukoCell® compared to those who received the classical procedure, the buccal mucosa graft urethroplasty.

## Design

This study will be a prospective, randomized, open-label and controlled clinical trial carried out in Hospital Universitari Doctor Josep Trueta from February 2021 until October 2029.

## Intervention and Methods

For 8 years and 9 months, a total of 132 patients diagnosed with a bulbar urethral stricture (>2,5 cm length) in the Hospital Dr. Josep Trueta will be recruited using a consecutive non-probabilistic method and will randomly be assigned with a ratio of 1:1 to undergo an urethroplasty using BMG grafts (group control) and urethroplasty with MukoCell® (by UroTiss Europe GmbH) as the intervention group.

**Keywords:** urethral stricture, urethroplasty, buccal mucosa graft, MukoCell®, complications

# INTRODUCTION

## 1. ANATOMY AND FUNCTION OF THE URETHRA

The male urethra is a narrow fibromuscular tube that conducts urine and semen from the bladder and ejaculatory ducts to the exterior of the body (1).

### 1.1. MACROSCOPIC ANATOMY

It has different portions depending on its anatomical path, it can be divided into prostatic, membranous, bulbous, pendulous, and navicularis fossa. The first two segments are parts of the mobile urethra (2).

The segments involving the prostate (prostatic urethra) and pelvic floor musculature (membranous urethra) are the posterior urethra, while the anterior urethra is formed from the segment fixed to the pelvic floor (bulbar urethra) and the segment that goes through the pendulous portion and glans penis (penile and glandular urethra) (3).

#### 1.1.1. PROSTATIC URETHRA

The prostatic urethra is the extension of the bladder neck, it is found in the thickness of the prostate and surrounded by itself, as well as by an inner circular layer of smooth muscle, which can be compromised in the pathological conditions the prostate can be found. Most commonly affected by benign prostatic hyperplasia (1,4).

The prostatic urethra is encompassed within the prostate gland. The widest part, contents de urethral crest, seminal colliculus, prostatic utricle and the orifices of the prostatic ducts, it measures 0.3-0.4 cm.

It goes up to the membranous urethra, supported inferiorly by the sphincter urethrae externus muscle and the perineal membrane, called the urogenital diaphragm (1).

The pre-prostatic urethra extends inferiorly from the urinary bladder and ends before entering the prostate gland. Embedded within the walls of the urinary bladder, it measures 0.5-1.5 cm in length.

When talking about the histology of this part it is formed by transitional epithelium, also called urothelium. The urothelium immediately surrounded by the glandular and stromal tissue of the periurethral zone of the prostate (5).

### 1.1.2. MEMBRANOUS URETHRA

The membranous urethra starts outside the prostate and ends just prior entering the bulb of the penis. Passes through the deep perineal pouch, the external urethral sphincter, and the perineal membrane. Found in the thickness of the urogenital diaphragm, formed by the Henle ligament in front, the deep transverse aponeurosis of the perineum behind, reinforced with the central nucleus of the perineum. The Cowper glands lie posterior to this portion

It has a length of 2-2.5 cm, the shortest and least distensible portion, and is surrounded by the sphincter system, formed by striated muscle, the main support for urinary continence in males. The external urethral sphincter muscle and the perineal membrane fix the urethra firmly to the ischial rami and inferior pubic rami, rendering this portion of the urethra susceptible to disruption with pelvic fracture (1,4).

In this part the histology changes as the urothelium turns into pseudostratified columnar epithelium. Thick layers of skeletal muscle are present at the level of the external urethral sphincter. Bulbourethral glands may be seen in a cross-section view (5).

### 1.1.3. SPONGY URETHRA (bulbar, penile, glandular)

It is the longest portion, with a length of 15 cm approximately. On its origin, it stands on the anterior part of the perineum to later be applied to the underside of the penis, penetrates the spongy sheath to find the bulb, the region that spans the corpus spongiosum of the penis, where it is covered by the bulbocavernosus muscle and becomes penile together with its spongy sheath (4).

It can be divided into the pendulous urethra and the bulbous (or bulbar) urethra. It occupies the whole length of the penis via the corpus spongiosum. The pendulous urethra is invested in the corpus spongiosum of the penis in the pendulous portion of the penis. It is wider initially when entering the bulb of the penis as well as in the glans of the penis, forming the navicular fossa, proximal to the urethral meatus, where the glands empty themselves.

The bulbous urethra is invested in the bulb of the penis, the portion of the corpus spongiosum that lies between the split corpora cavernosa in the superficial perineal space (1).

This last part is formed by pseudostratified columnar epithelium except for the terminal portion, which formed by stratified squamous epithelium. The corpus spongiosum is immediately surrounding this portion of the urethra (5).

### 1.2. EMBRYOLOGY AND HISTOLOGY

Almost all of it has its origins on the endodermal, excluding the most distal zone which is ectodermic. The urethra is a fibromuscular tube. The prostatic urethra is lined with transitional cell epithelium (urothelium). The membranous urethra is lined with stratified columnar and pseudostratified epithelium. There is also a vascular submucosa in the membranous urethra.

The penile urethra is enclosed by the corpus spongiosum and lined with the stratified columnar and pseudostratified epithelium with stratified squamous epithelium distally (1).

The wall is formed by three concentric layers (4):

- **Mucous tunic**: It is the layer that is lining the duct internally. It goes from the bladder neck to the urethral meatus. Formed by chorion and elastic fiber. At the same time, it can be divided into 3 different types (5):
    - Transitional epithelium (urothelium) → prostatic urethra
    - Columnar or pseudostratified epithelium→ membranous and anterior urethra
    - Stratified squamous epithelium → navicularis fossa and meatus

  We can find different glans, as well:
    - Intra-epithelial: can be found in the whole prostatic urethra.
    - Cowper's: in the perineum, and they flow into the bulbo-membranous urethra.
    - Littre's: they lead into de Morgagni gaps.
- **Vascular layer**: it can be called corpus spongiosum. It is an erectile tissue; found in the wholesome of the urethra, except for the posterior part, which is the prostatic and membranous portion.
- **Muscular layer:** It is formed by smooth and longitudinal circular fibers, which are an extension of the bladder muscles.

### 1.3. VASCULARIZATION AND INERVATION

The anterograde or arterial supply of the urethra is a source of the internal pudendal artery which gives branches to the urethral artery and bulbar artery, which run the length of the penis, and to the glans where they anastomose with the dorsal artery.

The prostatic urethra is supplied by the inferior vesical artery, and the branches penetrate the prostate and the bladder neck in superior-lateral positions.

The bulbourethral artery supplies the membranous and bulbar urethra, whereas the pendulous urethra is supplied by the deep penile artery, a branch of the internal pudendal artery.

In the retrograde blood supply (or venous system) we have the urethral and bulbar veins that run alongside their respective arteries, then they join in the bulb to form a common urethra-bulbar vein which drains to the pudendal vein. The prostatic and membranous urethra drain to the obturator and the internal iliac nodes (1,6).

Lymphatic drainage from the spongy urethra drains to the deep and superficial inguinal nodes (1).

## 2. CAUSES/ETIOLOGY OF URETHRAL STRICTURE DISEASE

Usually, the bulbar strictures are the most common (almost 50%), followed by penile strictures (30%), and strictures of the navicularis fossa (20%).

The majority of the urethral strictures in male adults are iatrogenic (45%), and they occur as a result of urethral manipulations such as traumatic indwelling catheterization, transurethral interventions, correction of hypospadias, prostatectomy, brachytherapy, etc.

30% of them are considered idiopathic, and in some of these cases, there must have been a forgotten minor trauma in the past.

Another of the main causes of urethral stricture is a traumatic urethral rupture associated with pelvic fracture. These types are the ones with strictures in the posterior urethra, which are rare, just like the ones due to radiotherapy for prostate cancer, as it is consider one of the most common effects of radiotherapy. The post-traumatic strictures are usually caused by work or traffic accidents, and are due to two main mechanisms:

- Direct injury from bone splinters in the event of pelvic bone breakage.

- Rupture of the membranous urethra due to shear, because of its firm anchorage by the urogenital diaphragm.

We may mention the stricture post-ischemia as well, that is observed after the probe during an extended time or after the surgery (7).

Other causes may be bacterial urethritis (20% of the cases can lead to those), most of them may be related to untreated gonorrhea; also, there is another inflammatory disease which is balanitis xerotica obliterans associated with distal strictures. The ones caused by infections are usually due to chronic or recurrent infections over the years. The infection causes are less frequent than in the past, thanks to an early diagnosis, especially with gonococci urethritis, and *Chlamydia* (3,7,8).

When talking about the anterior urethral strictures, the bulbar ones are more commonly produce by idiopathic (40%), iatrogenic, traumatic and inflammatory causes, in this order; whereas in the penile strictures the most predominant are the iatrogenic and inflammatory, both with a presentation of 40%, followed by the ones caused by idiopathic and traumatic causes. Even though strictures in the bulbar urethra predominates over other locations, strictures related to hypospadias and lichen sclerosis (BXO) are generally located in the penile urethra, while the traumatic stenoses tend to be bulbar and posterior urethra (8,9).

*Table 1. Causes of urethral stricture* (3)

| **Causes** | | **Incidence** |
|---|---|---|
| **Iatrogenic** | Transurethral prostate resection<br>Radical prostatectomy<br>Hypospadias correction<br>Indwelling catheterization<br>Cystoscopy | 45% |
| **Bacterial urethritis** | | 20% |
| **Lichen sclerosis (BXO) and atrophic** | | 5% |
| **Idiopathic** | | 30% |

Geographical setting, socioeconomic factors and access to healthcare can affect the stricture etiology. In developed countries, the most common etiologies of urethral stricture are idiopathic, followed by iatrogenic. Late failure of hypospadias surgery and stricture resultant from endoscopic manipulation are common iatrogenic reasons. In developing countries, the most common cause is trauma, as a high rate of road traffic injuries, less developed trauma systems, and so on (10).

## 3. PATHOGENESIS

All strictures result from an injury to the epithelium of the urethra (urothelium) or the underlying corpus spongiosum which ultimately ends up causing fibrosis due to the healing process. When there is a lesion that affects the urethra, it will lead to a scar, where there is going to be a substitution of the normal tissue into a conjunctive tissue and abundant collagen. As a result, this leads to a loss of elasticity, contractility, and reduction of urethral lumen (4,9).

The pathological changes associated with strictures are that the normal pseudostratified columnar epithelium is then replaced with squamous metaplasia and next, we can see, what has been described as the creep phenomenon where small tears appear in the metaplastic tissue from the high voiding pressures of the urine behind it, which ends up causing a fibrosis reaction in the spongiosum and the stricture can creep proximally and lengthen. This fibrotic process can progress until there is an existence of the narrowing lumen (9).

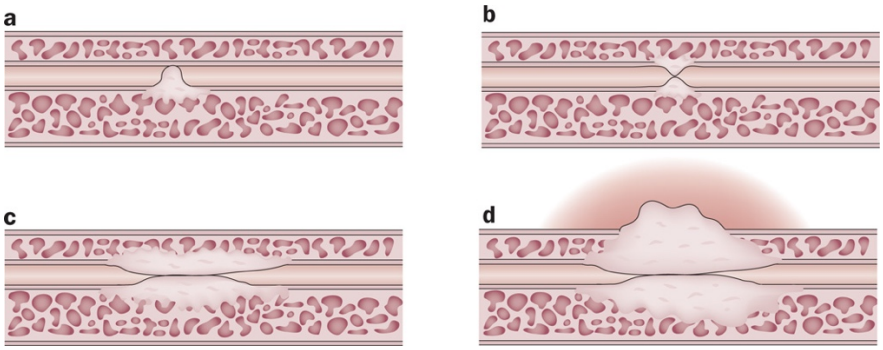


*Figure 1. Stricture pathogenesis* (9)

This process is characterized by changes in the extracellular matrix in the stricture urethral tissue. In these cases, there is a change in the tissue, and it is exchanged for dense fibers interspersed with fibroblasts and a decrease in the ratio of type III or type I collagen. There is a

decrease in the ratio of smooth muscle to collagen, and changes in the synthesis of nitric oxide in stricture urethral tissue.

Usually, anterior urethral strictures are due to trauma or infection, that results in spongiofibrosis (density of the stricture), in this whole process, the corpus spongiosum becomes fibrosed, also involving the tissues outside of the corpus spongiosum at the end.

Posterior urethral stenoses are a result of an obliterative process that causes fibrosis, such as iatrogenic injuries from pelvic radiation or radical prostatectomy, and even distraction injuries after traumas (pelvic fractures), that is why they are considered as contractures or stenoses, rather than true strictures.

## 4. SIGNS AND SYMPTOMS

The main symptoms of urethral strictures are those of obstructed and irritated micturition. Increased urination time and a feeling of incomplete bladder emptying plus increased micturition frequency and urgency (3).

These are the major symptoms for which the patient may consult the specialist. The lower urinary tract symptoms include (10,11):

- Hesitancy
- Intermittent stream
- Decreased caliber of the urine stream
- Incomplete emptying of the bladder
- Nocturia
- Pain with voiding
- Urinary retention

Most patients present with slow and progressive deterioration of the urinary stream leading to a feeling of incomplete emptying as obstruction progressively develops. The most severe cases may present hematuria or even some may present recurrent urinary tract infections and its sequelae: epididymitis, rising post-void residual (PVR) urine, or decreased force of ejaculation (12).

Other symptoms may be urinary spraying or dysuria. Rare sequelae of untreated stricture may include bladder calculi, urethral abscess, urethral carcinoma, and chronic kidney injury from

obstructive uropathy. Sometimes secondary to a superinfection, there is acute retention of urine, where we should do a placement of a cystostomy catheter (7,10).

## 5. DIAGNOSIS OF STRICTURE

In most of the patients, it is enough with a good clinical review, a uroflowmetry, a RUG and a VCUG to make the diagnose; after there is the possibility to do a diagnostic-therapeutic endoscopy, which is called intern endoscopic urethrotomy (13).

### 5.1. UROFLOWMETRY

This is a simple and safe test, ideal to do the follow-up of the strictures. It gives us information about the voiding volume, flow curve, and peak flow.

It is part of the initial investigation in patients with lower urinary tract symptoms. Patients presenting urethral stricture the peak flow rate is typically low, but the flow pattern is characteristically flat.

This flow pattern is almost pathognomonic of urethral stricture. The patients would usually present an obstructive voiding pattern on uroflowmetry studies and, it can appear a high postvoid residual volume suggestive of incomplete emptying (9,12).

It is a suggestive test that indicates the presence of a urethral stricture as we can see the graphic registered flat and rigid in the voiding curve. We need at least a bladder volume of >150-200 ml so that the test has a value. The maximum volume is usually very low and persistent. We consider that a peak flow less than 10 ml can tell us the presence of obstruction.

It is a non-invasive test, cheap, easy to perform. With it, we can control the evolution of the patients already diagnosed and treated (7,13).

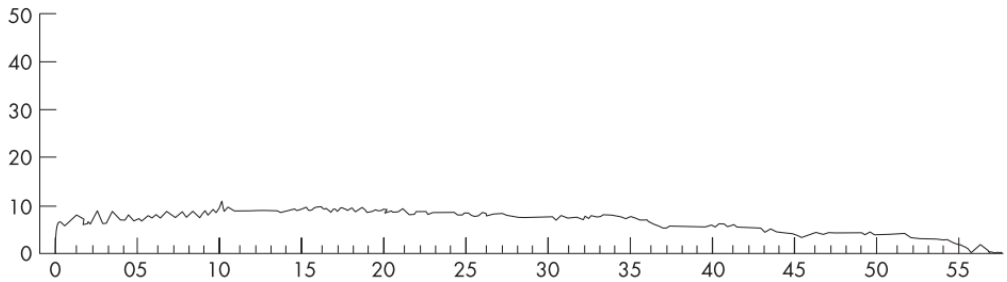


*Figure 2. The flow pattern of a patient with a urethral stricture* (12)

### 5.2. RETROGRADE URETHROGRAM (RUG)

This test is the most important, amongst them all, which makes it the gold standard. It shows the exact site and length of the stricture and most of its potential complications. It is used to find and assess the location, and severity of the stricture as well (9).

First of all, the scout film assesses bony structures, and the presence of calcified urinary tract pathology. The contrast, 20-30 mL of water-soluble iodine, is injected through the meatus of the penis, and some pictures are taken to see the stricture as itself (14).

In this case, after emptying the bladder, the patient must be in a specific position laying on the bed, in lateral decubitus with the lower limb flex to 35-45º degrees, in an oblique position to maximize the visualization of the bulbar urethra. The radiographic technique and proper oblique positioning are critical and basic to not underestimate the length of the stricture.

Then the contrast is gradually introduced, in a slow way. Upon here a proper study of the anterior urethra can be made. After filling the bladder and the urethra, the patient is asked to urinate voluntarily, and as this goes on, multiple radiological shots are taken during it. This way the study of the posterior urethra can be made properly (12,14).

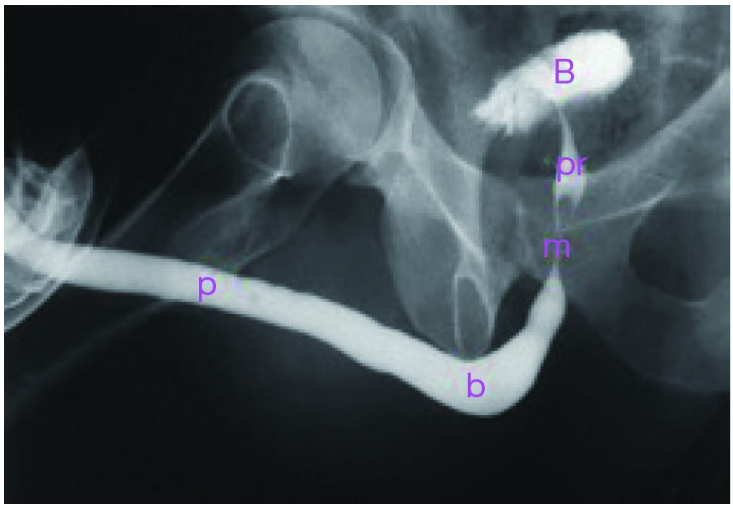


*Figure 3. Normal RUG demonstrating the male urethra anatomy* (14)

*B: Bladder; pr: prostatic urethra; m: membranous urethra; b: bulbar urethra; p: penile urethra*

### 5.3. VOIDING CYSTOURETHOGRAM (VCUG)

It is another technique, and it is an anterograde urethrogram. In this case, this is an exam in which the patient's bladder is filled with contrast, afterwards images of the bladder and the kidneys are taken, while they fill, and the patient urinates. This test is excellent for assessing posterior urethra, where the bladder neck and prostatic urethra are distended (14).

It can be useful for:

- Obliterative or near-obliterated strictures, where the contrast does not pass through the stricture, so the contrast can be passed through the supra pubic (SP) tube and then take the urethrogram.
- Distal penile strictures, which can be difficult to image in a retrograde way (12).

### 5.4. URETHROSCOPY

A cystoscope is introduced through the urethra to evaluate it, this way the stricture can be seen endoscopically and the percentage of obliteration that the patient may present is measured.

The stricture can be evaluated through the urethral meatus, alternatively, it can be done through a suprapubic access.

Sometimes it can be used at the same time as a treatment for the urethral stricture. In those cases a pediatric cystoscope with a Sachse knife is used, so in case it is necessary at that same moment, an endoscopically intern urethrotomy could be realized (13).

### 5.5. ULTRASOUND EVALUATION

The urethral echography is a technique used to complete the study. The urethra is seen as a hypoechogenic line, with a diameter between 8-10 mm, after the insertion of physiological serum through the Foley catheter (15).

Ultrasound evaluation may show thickening of the bladder wall associated with longstanding outflow obstruction, and a presence of residual urine. If there are both of them present, an ultrasound scan of the kidneys should be the next step to look for signs of obstructive uropathy. While looking at the bulbar urethra, the echograph may be positioned in a sagittal way through the perineum (12,15).

The ultrasound can assess the extent of spongiofibrosis, especially in the bulbar urethra (7).

The tests involving images are important, because they not only determine the characteristics of the stricture, but also evaluate the urethra, proximal and distal, to the stricture and ensure that all diseased portions of the urethra are included in the repair (9).

### 5.6. MRI and CT EVALUATION

The use of the MRI is more suitable in the cases of a stricture urethra caused by a tumor. In this case, this technique would be used to show the possible spreading of the tumor to other tissues such as the corpora cavernosa. It can also be used to evaluate the result of a possible trauma to the posterior urethra.

Likewise, the CT used in the voiding phase gives us information about the presence of fistulas in the urethra (15).

## 6. TREATMENT

A brief summary of different treatments used in urethral strictures can be found in annex 1.

The details of each treatment depending on their localization can be found as follows:

### 6.1. ANTERIOR URETHRA: BULBOUS PORTION

*Table 2. Bulbar urethral strictures treatment*

| **Stricture and length** | **Treatment** |
|---|---|
| Short bulbar stricture <0,5 cm – 1 cm (without spongiofibrosis) | Urethral dilation<br>Internal urethrotomy |
| 1-2 cm stricture | End-to-end anastomotic urethroplasty/EPA |
| 2-3 cm stricture | Augmented end-to-end anastomotic |
| Strictures larger than >3 cm | Urethroplasty using dorsal or ventral BMG |
| Severe strictures, larger than >6 cm | Urethroplasty in two stages |

### 6.1.1. Urethral dilation

It is the passage of calibrated instruments, such as urethral dilators. They are straight in their whole length, with a hockey stick curve at the end. They are calibrated according to the French system, which relates the size of the urethral dilator to the urethral circumference in millimeters. The normal caliber of the urethra is about 24-26 (French) in the meatus zone, and wider up in the penile urethra, which is about 36 Fr, and it becomes narrower again up in the posterior urethra (12).

In these cases, a series of dilators are used from thinner to wider size, passing them through the stricture to restore the normal caliber.

It is rarely curative, so it has been seen that if the procedure has to be repeated, and even the first time, it is expected to cure about 50% of the short urethral strictures.

- **Urethral stents**: Another modality used in opposing forces of wound contraction after internal urethrotomy or dilation. The UroLume®, a permanent stent, is made of an ally, to be integrated into the wall of the bulbar urethra with minimal spongiofibrosis. The stents must only be applied in the bulbous urethra. Temporary stents need to be exchanged every 3-12 months, being more suitable for men with posterior urethral obstruction. They tend to have limited use and high rates of complications (9,16).

### 6.1.2. Internal urethrotomy

This endoscopic technique uses a cold knife to make an incision to release the stricture scar tissue and then allows it to heal by secondary intention, although there is no consensus about leaving a catheter, as well, as the number of days the catheter should be left.

Usually, those strictures at the bulbous urethra, with less than 1.5 cm in length and not associated with dense deep spongiofibrosis, can be treated with internal urethrotomy.

There are huge success rates in the literature for DVIU, although they range from 10-80%, depending on the times of the follows ups.

One of the most common complications in this technique is the recurrence of stricture. Other less commonly noted are bleeding, and extravasation of irrigation fluid into the perispongiosal tissue (16).

### 6.1.3. Urethroplasty

- **End-to-end anastomotic urethroplasty**

It is the excision of the urethral stricture and join of the two healthy ends of the urethra on either side, together again to restore continuity and caliber. During the anastomotic urethroplasty the stricture is excised transversal and sutured back together, it must be taken as distal as possible to minimize any tension, as it may produce some limitations and loss of elasticity.

Traditionally the end-to-end anastomosis was used in the bulbar stricture with a length of <2.5 cm, due to the tension that can cause in the future. Success rates in the bulbar urethra goes from 91-95%. Altogether it can only be performed in the bulbar urethral stricture, and in strictures measuring under 4 cm in length.

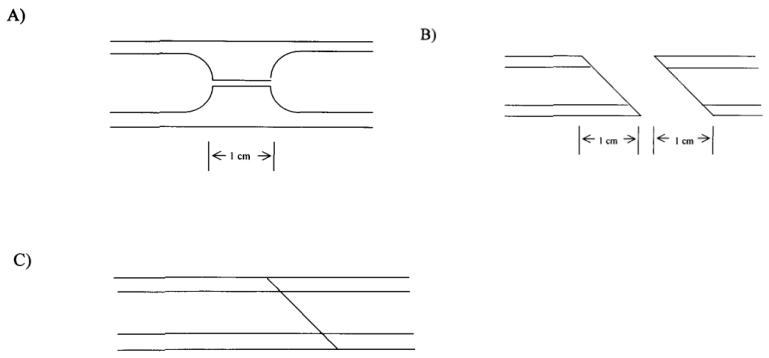


*Figure 4. EPA (excision and primary anastomosis)* (17)

*A) 1 cm urethral stricture. B) Stricture is excised and opposing 1 cm spatulations are made into healthy urethra. C) Urethral ends are anastomosed, resulting 2 cm urethral shortening.*

- **Augmented end-to-end anastomotic**

This technique is usually indicated in those cases that could cause further shortening of the bulbar urethra, due to the loss of tissue and length. When resecting the normal tissue, a gap may be left, then this could be augmented with a BMG.

In this technique, the affected length of the urethra is removed and the remaining healthy urethra anastomoses to form either the floor or roof strip. The next step in the procedure is to open the urethra 1 cm through the remaining stricture, distally and proximally. Finally, the graft is placed, preferably BMG, on the urethral wall opposite to the anastomosis, so that it will be slightly shortened. It is important to remind that preputial mucosa graft can also be used (17).

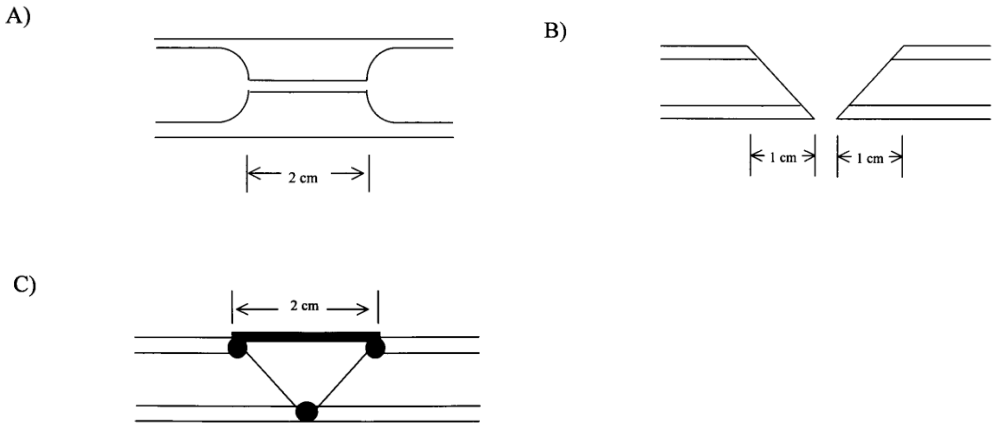


*Figure 5. Augmented anastomotic urethroplasty* (17)

*A) 2 cm urethral stricture. B) Stricture is excised and 1 cm ipsilateral spatulations are made into healthy urethra. C) Urethral ends are anastomosed as roof/floor strip and resultant contralateral defect is corrected with 2 cm onlay graft/flap, resulting in 2 cm urethral shortening.*

- **Urethroplasty with free grafts**

Grafts do not have its own blood supply, so it relies on the host bed for passive diffusion of nutrients during the first 48-72 hours, with a process called imbition During the 3-5 days the revascularization starts, and on the 7$^{th}$ day there is a lymphatic and blood vascularization. Extra genital skin grafts are usually preferred, especially with lichen sclerosis, such as the buccal mucosa graft.

There are different types of grafts successfully used for urethral reconstruction (16):

- Full-thickness skin graft
- Bladder epithelial graft
- Oral mucosa graft: which can be taken from the cheek (buccal), lip (labial), and the undersurface of the tongue (lingual).
- Rectal mucosa graft
- Preputial mucosa

Both preputial and buccal mucosa are composed by stratified squamous epithelium, non-keratinized, formed with two layers, the basal stratum (2-3 cells thick), and the stratum spinosum, and the lamina propia instead of dermis. The difference lies under the mucosa where in preputial mucosa smooth muscle fibers (Dartos) are found, whereas in the buccal mucosa minor salivary glands are found.

The buccal mucosa has a stratified squamous epithelium, non-keratinized, and a lamina propia with a wide of 0,5 mm. The epithelial cells from the intermediate stratum spinosum and the superficial stratum, linked together, provides a firm epithelium urine resistant.

When using the oral mucosal grafts, there is a favorable vascular characteristic, called the panlaminar plexus. The mucosa is firmly vascularized, which helps the rapidly changes and the good inosculation. This type of graft can be thinned somewhat, providing enough of the deep lamina, carried to preserve the physical characteristics and vascularization. BMG is getting better because of its thick and highly vascular spongiosum tissue. After 25 days, the epithelium starts regenerating completely (16,18,19).

At the same time, they are readily available in all patients, concealed donor site, low morbidity after harvesting, no long-term morbidity, and after all, they are hairless and compatible with a wet environment, and as we said before they have a thin lamina propia vascularized, as well as an elastin rich epithelium (20).

**Buccal Harvest**

There are known several relative and absolute contraindications to harvesting these grafts.

*Table 3. Normal and pathological oral conditions* (20)

| **Normal oral conditions** | **Pathological oral conditions** |
|---|---|
| Ephelis (cutaneous freckle)<br>Fordyce granules (ectopic sebaceous glands)<br>Linea alba buccalis (white streak on buccal mucosa following the occlusal plane)<br>Morsciatio buccarum (cheek chewing) | Leukemia<br>Leukoedema<br>Mucositis associated with head and neck radiation therapy, chemotherapy, and cancer surgery<br>Pemphigus vulgaris<br>Mucous membrane pemphigoid<br>Erythema multiforme<br>Oral lichen planus<br>Recurrent aphthous stomatitis (canker sores) |
| The first column list oral conditions that may delay oral mucosa harvest until site conditions improve.<br>The second column lists oral conditions that would be strict contradictions for oral mucosa harvesting. | |

The mobilization of the graft is relatively contradicted if the patient presents: gingival infections evolutional, history of oral cavity carcinoma, is taking up anticoagulants, and previous history of local irradiation. Other contradictions to be looked for are metabolic, recent local infection, and active smoking, which is an absolute contraindication (21).

The buccal substitution urethroplasty is performed with a two-team approach: as one harvests the BMG, the other team performs the perineal dissection (11).

A surgical pen is used to outline the extent of a graft, keeping several millimeters away from Stenson's duct. Then a local anesthetic is injected to dissect the layers from the underlying muscle tissue, usually Bupivacaine 0,5% with epinephrine is injected underneath for analgesia and intraoperative hemostasis. The graft is 2,5 cm wide and as long as needed, it is incised by a scalpel and limited to the full thickness of the mucosa. Creating the dissection plane through the submucosal adipose tissue layer superficial to the buccinator muscle.

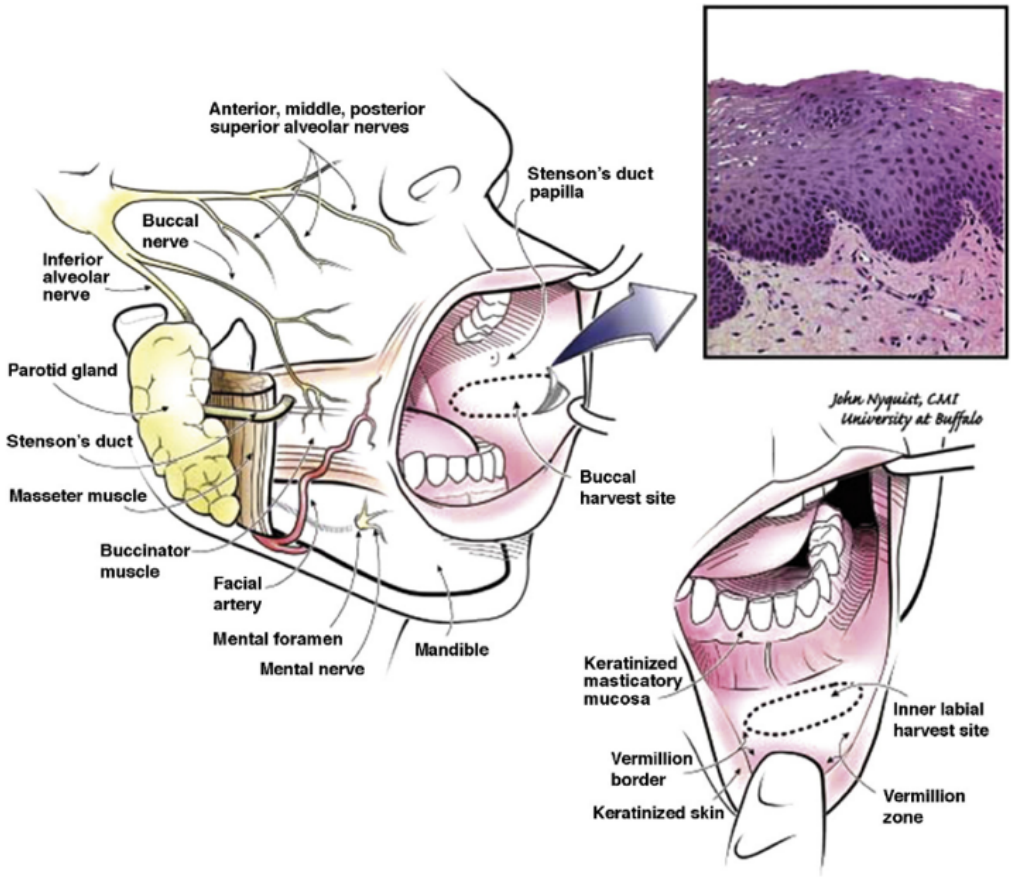


*Figure 6. Buccal mucosa harvest* (20)

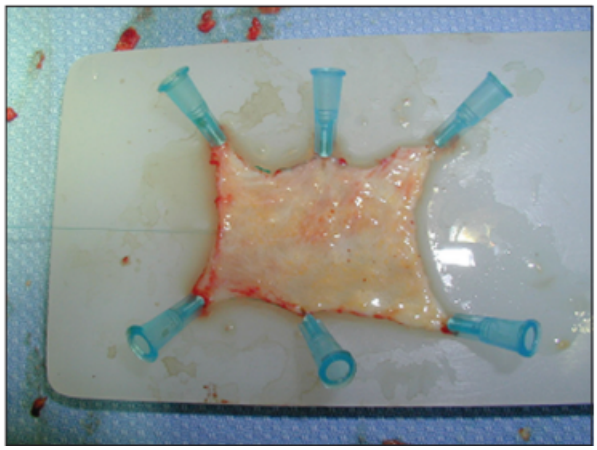

*Figure 7. Buccal mucosa graft prepared* (11)

Primary closure is accomplished with a single layer of 4-0 absorbable sutures, the graft is put into normal saline and is stretched on a hard surface, and excess of fat or muscle fibers are trimmed from the graft (11,22).

A systematic review of closure or non-closure of buccal mucosa graft site with 269 patients, claimed no difference at 6 months between the groups in: pain, numbness, mouth tightness, and restriction of oral intake (23).

The main complications of buccal harvesting include salivary duct and nerve damage, and after there can be pain, numbness, bleeding, infection and swelling, there can be scarring and contraction which leads to tightness affecting jaw opening and speaking disorders.

Another complication of buccal mucosa graft harvesting is the limitations of its availability in patients that may present recurrent strictures, or in patients who have limited jaw opening or maxillofacial disorders.

Other long-term consequences include oral health, scarring, chronic ulcers due to repeated bites on scar bulges, impaired lip mobility, permanent salivation, oral stenosis, facial deformities, and diminished facial expressions. One of the late consequences, that results from chronic irritation and inflammation, is the risk increase of oral cancer.

**Where to locate the graft?** (Annex 2)

- Dorsal Onlay: Barbagli technique

The urethroplasties with free flaps have usually been used for bulbar or penile strictures with a length of >2.5 cm. In these cases, we need to use external tissue to increase the urethra caliber. During the '90s the buccal mucosa grafts became popular in the use as a treatment of these kind of strictures.

It has been seen that the dorsal placement of the BMG is simpler and safer in the distal part of the bulbous urethra, in this procedure a full mobilization of the urethra is needed, rotating it 180 degrees to adjust the BMG dorsally. In this case, it is quilted to the corpus cavernosa and sutured at both ends, the urethra is rotated back to its original position covering the graft area.

The main complications in this technique are erectile dysfunction, ejaculatory dysfunction, infection of the wounds, UTI, fistulas, neurapraxia, and incontinence (18).

- Dorsal Inlay: Asopa technique

Asopa has a shorter operating time and it is technically easier. Although, the results of curation are more or less the same, with the dorsal onlay an 88%, and inlay with 86.4% rate of success (24).

Asopa modified the technique, in such a way, where it opens the ventral urethra, instead of releasing the dorsal one. The stricture can also be accessed at the dorsal level, where the graft is sutured in the area of dorsal tissue resection (15).

Nowadays, we use this technique in those cases where the plasty goes from the penile urethra up to the peno-bulbar angle (21).

*Table 4. Advantages and disadvantages of dorsal onlay and inlay*

| **Advantages** | **Disadvantages** |
|---|---|
| Dorsal longitudinal stricturotomy bleeds less and can be done in all portions of the bulbar urethra.<br>Avoids sacculations<br>Non-circumferential of the urethra | Full mobilization of the urethra is needed.<br>More risk of damaging bulbar arteries in proximal strictures, which may contribute to erectile dysfunction.<br>There can be damage penetrating cavernous collateral arteries.<br>Urethral plate needs to be at least 1 cm wide |

- Ventral Onlay

This technique has been rather useful and efficient where the spongiosum tissue is thicker and better vascularized (18).

*Table 5. Advantages and disadvantages of ventral onlay*

| Advantage | Disadvantage |
|---|---|
| No mobilization of the bulbar urethra is needed<br>Less danger of damaging bulbar arteries or penetrating collateral cavernous arteries.<br>Faster and easier than a dorsal approach. | Bleeds more than a dorsal approach, mainly in the proximal aspect of the bulbar urethra.<br>Stitches are more difficult to place in very proximal strictures.<br>Not possible in distal strictures – lack of spongy tissue.<br>Risk of diverticulum |

**Step by step urethroplasty** (Annex 2)

The procedure is done in the normal lithotomy position of the patient. BMG in urethroplasties can be placed whereas dorsally or ventrally as explained before. Multiple studies have shown that either dorsal or ventral-onlay BMG has both, good blood supply and mechanical support.

It begins with the placement of a traction wire on the tip of the glans and a guidewire in the bladder. Methylene blue is infused into the urethra. A probe of 20 Fr up is placed up to the stenosis, to identify it. Then, an incision is made into the bulbocavernous muscles dividing and, opening the midline, exposing the bulbar urethra.

The buccal mucosa graft is harvested from the cheek using a two-team approach with the donor site and closed with 4-zero polyglactin interrupted stitches.

Depending on the location of the graft we may or may not do a full mobilization of the urethra, rotating it 180 degrees, as explained before in the cases of dorsal onlay.

This way, the urethra is opened with the help of a scalpel, fixing the urethra at the ends with a Babock clamp. Next, some deep presentation threads are placed in each centimeter to hold it open. The urethra is opened with scissors until a healthy urethra is found proximally to the stricture. Then the graft may be sutured at the proximal level, with separate and absorbable stitches at the edges of the urethra, once the probe is placed, the other side of the grafts is sutured to the urethra.

The corpus spongiosum is closed ad integrum with a suture of the same thread. Finally, the three planes will be closed over a drain and a 16 Fr probe placed (18,21).

**Post-operative care**

When using grafts, a urinary diversion must be guaranteed the first days, so a urethral catheter, 20 Ch will be placed. In all cases without further complications, the standard durations is about 8 days.

The first post-operative follow-up will take place on the eight day, where a VCUG can be performed through the catheter.

Antibiotic therapy will be administered for 5 post-operative days (15).

- **Urethroplasty using pedicled flaps**

A flap is a mobilized tissue that maintains its original blood supply and when talking about the success of the flap, the word flap survival is used. The most used ones are the penile skin island flap on dartos pedicle or dartos fascia flap.

Normally the flaps of the foreskin or the skin of the dartos layer of the penis, which are highly vascularized, are the ones mobilized, which depending on their length can be carried up to the bulb. The flaps are usually used when the conditions in the urethra are not favorable for graft use, or when there is extensive scarring, or active infection, previous radiotherapy or when the stricture is too long or trans-sphincteric (8).

This technique relies on the blood supply from Buck's fascia and can be used along the entire penile and bulbar urethra (9).

We have to bear in mind the fact that scrotal skin flaps have hair follicles, so they need to be removed at first. This is one of the main drawbacks of this technique, together with the sacculations (15).

#### 6.1.4. MukoCell® technique

Tissue-engineered devices are biological-biomaterial combinations in which some component of tissue has been combined with a biomaterial to create a device for restoration or modification of tissue or organ function (25).

There are some clinical studies showing that the cells may be introduced to biological or synthetic scaffolds. The ones used on acellular human dermis or on collagen matrix led to good acute stage tissue integration. It is important, that the tissue-engineered graft becomes well vascularized.

The problems regarding the different types of scaffolds are:

- Organic matrices → potential risk of infection, and antigenic complications.
- Synthetic matrices →functional, mechanical, and structural problems.

Another type of scaffold is a DED (acellular de-epimerized) which has been developed reconstructing human skin for clinical use in patients with burns. This same DED carrier matrix can be used to develop TEMB suitable for substitution (26,27).

A common way of tissue engineering is the use of acellular matrices, which are protein scaffolds made mostly of collagen. These can be enhanced by adding autologous mucosal cells to the matrix, making a biocompatible tissue replacement matrix.

In this case, buccal mucosa is taken from the patient and grown in the laboratory, some weeks later, sheets of tissue-engineered oral mucosa are created. Some studies have shown a success rate of 83-90% for BMG tissue engineered (28).

MukoCell® is an autologous tissue-engineered oral mucosa graft, TEBM product. In this case a small piece of the patient's buccal mucosa is taken as a tissue biopsy under local anesthesia (29).

Keratinocytes and fibroblasts are then isolated and cultured, seeded, and expanded onto a surface of biocompatible scaffold, as it is a product that comes in prepared for the seeding of the extraction, with a solution set for the cultured cells. Afterwards, cell culture will be performed according to the manufacturer's instructions.

In this case, the cells are used for the manufacture of the autologous tissue-engineered graft in Germany in their certified cell cultured GMP (Good Manufacturing Practice) laboratory (UroTech). After three weeks the process is complete and the graft is delivered to the hospital in a sterile container, where then it can be used for the urethroplasty. MukoCell® GmbH has a tissue engineering platform that consists of different cell types and structures, which offer the maximum adjustment possibilities in terms of shape and size, as well as a high-level resistance against urine (26,30).

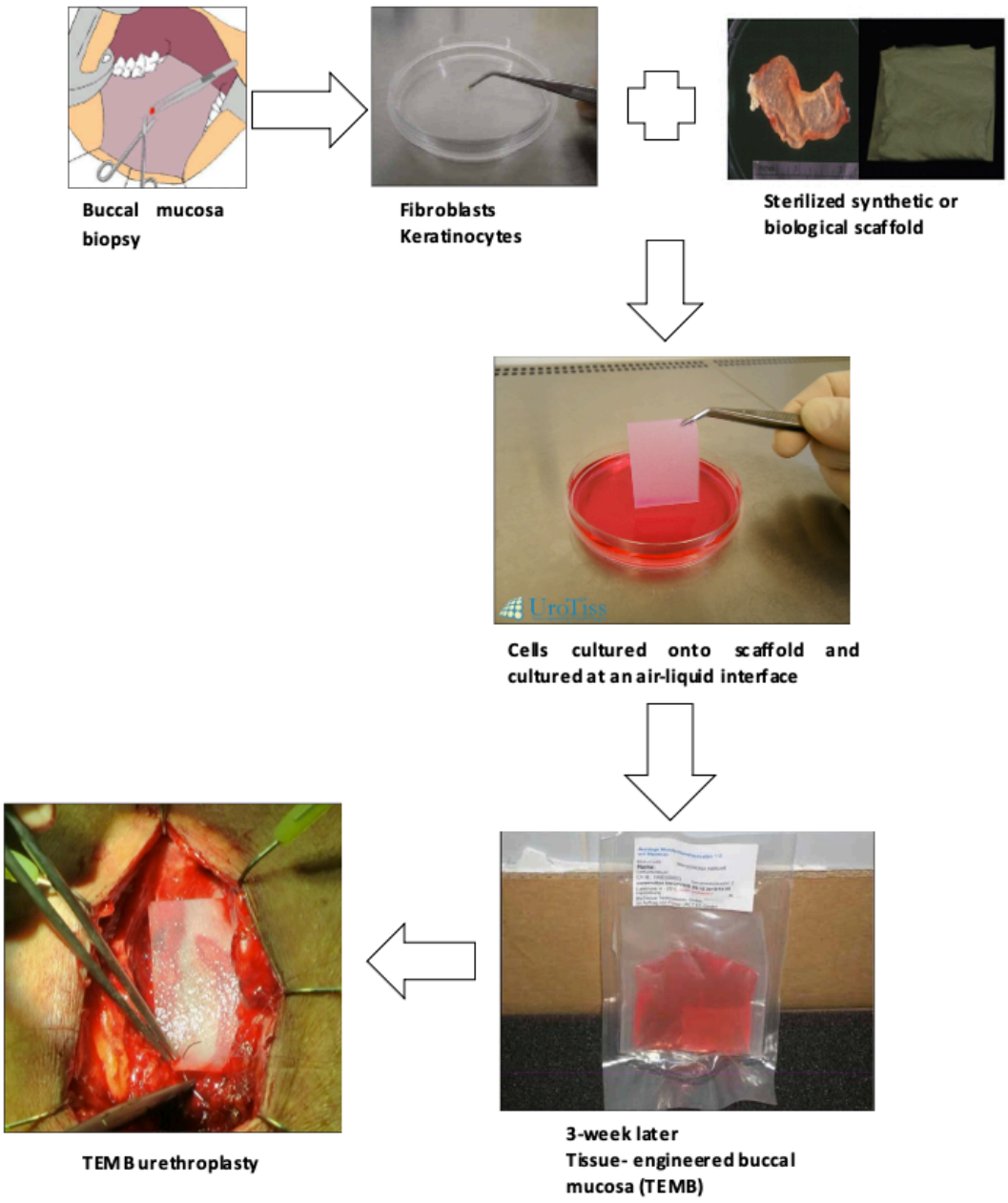


*Figure 8. Tissue-engineered buccal mucosa procedure*

This type of material would reduce and be safer in the subject of the transmission of bacterial, viral and other infectious agents that may concern us. In an article from Barbagli *et al*., 12 bulbar urethroplasties were done using this TEMB technique, which appeared to have a remarkable rate success. This technique is now starting to be used in all the anterior urethroplasties, as it may reduce the number of infections, and the problems related to harvesting buccal mucosa, reducing complications, morbidity, and other risks of transmitted diseases (31).

### 6.2. ANTERIOR URETHRA: PENILE AND NAVICULARIS FOSSA

The urethral dilation or the DVIU are both main techniques used in the treatment of the anterior urethral stricture.

In 1968 Orandi described his ventral, longitudinal flap for penile urethral strictures using a lateral pedicle with good results. The main disadvantage of this flap is the fact that if it involves part of the pendulous or bulbar urethra, hair-bearing skin is involved in the reconstruction, which at the end can lead to infections and stone formation. It is used in those strictures due to traumas, instrumentation, catheters, infections or other causes. Some of the complications are penile hematoma, necrosis, fistula, and glans torsion (32).

They are classified as simple, the ones which are idiopathic, or with a urethral plate caliber >6 Fr; or complex if they present LS or previous hypospadias repair, full thickness fibrosis, or full circumference graft is required.

Usually when talking about pendulous urethral strictures, the Johanson urethroplasty is the one used. There might be the consideration whether of a one-stage urethroplasty, or a first stage Johanson urethroplasty, using or not BMG with a dorsal onlay, followed by a second stage Johanson. When LS occurs in the urethral plate, foreskin and penile skin may be affected so severely that reconstruction may have to be performed in multiple stages, those cases are complex penile strictures. In these cases, and because of the massive destruction of the urethral plaque made by this disease, a urethral reconstruction cannot be proceeded (11).

During the first stage, we may proceed with the extirpation of the buccal mucosa graft, and the excision of the damaged tissue that the urethra presents. We may then leave it from 6 up to 12 months. After on the second stage: tubularization, almost one year later, and re-intervention of the patients doing a closing surgery (Duplay's type) were the dartos fascia is the one used as a protection for covering it.

The main complications are fistulas, glans dehiscence and meatal strictures.

### 6.3. POSTERIOR URETHRA

As grafts and flaps are more used in anterior urethral stricture, in the defects of the posterior urethra, end-to-end anastomosis are usually performed. In these cases, an endoscopic realignment attempt must be proceeded, before collocating a urine drain (via suprapubic or urethral), and a delayed surgical repair will be performed. Most of these are due to pelvic

fracture urethral injury, so in this case is proceeded with an excision of the scar tissue and reanastomosis of the healthy urethral segments, with a previously urethral realignment before.

In pelvic fracture urethral injuries, we use RUG, VCUG or endoscopic assessment for preoperative planning of delayed urethroplasty. In the posterior urethral disruptions, we expose the bulbo-membranous urethra, mobilize the anterior urethra distally, transect the urethra and excise the scar of fibrosis, spatulate both urethral ends, then a tension-free anastomosis is performed, and the repair is stented.

In the case of bladder neck contracture or vesicourethral stenosis a dilation may be performed, bladder neck incision or TURBNC after endoscopic prostate procedures.

# 7. COMPLICATIONS

## 7.1. SHORT-TERM COMPLICATIONS

**Infection of the wounds:** it can lead to warm skin, unpleasant odor, fever and chills, aches and pains, nausea, and vomiting.

**Infections and urethritis:** We have to bear in mind that the infections can be exogenous or endogenous, and that their evolution will end up producing urethritis and abscesses. There are a number of measures to take to reduce the appearance of infection, which are:

- Ensure correct viability of the graft tissue.
- Avoid ischemic tissue graft
- The use of antibiotic prophylaxis
- Avoid the presence of hematomas or changing of the dressing to frequently.
- Correct diversion to avoid the passage of urine through the suture area. Which in this case the best would be a thick suprapubic catheter.

**Bleeding:** Found in different points: in the open corpus spongiosum, in the line of the urethral anastomosis, in genital dissection in flaps or grafts, or in lesions with insufficient hemostasis of perineal or bulbar arterial vessels. We have to keep in mind that it is the most imminent complication, and it depends directly on the hemostatic technique used (2).

### 7.2. LONG-TERM COMPLICATIONS

**Restenosis:** It is the most frequent one, and it does not depend on the technique used. The appearance of restenosis indicates that there has been a failure in the surgical technique. When talking about the most used technique with grafts, the urethroplasty with BMG is the most common one. They are suspected when there are recurrent urinary infections, or the patient shows symptoms of obstructed and irritated micturition.

Some papers can be found about the frequency of restenosis in this type of technique, such as in Martínez- Piñeiro *et al*. it has been seen that 16% of the patients required additional surgery. Given 53 urethroplasties with BMG, six cases had recurrence of strictures, three of which required intervention. In Andrich *et al.*, 128 patients underwent surgery and 11% of the BMG urethroplasties presented restenosis. In an article by El-Kassaby *et al*. there were a series of 8% cases of restenosis (33,34).

**Fistulas:** Described as the abnormal passage of urine from the urethra to the skin, it is usually the most frequent complication in hypospadias surgery, appearing in 20% of the times. In one-stage urethroplasties, they tend to be less than 10%, but it can go as high as 40%. They do not usually close spontaneously. They can be the origin of devascularization of a pedicled graft and can even be due to erections during the immediate postoperative period with dehiscence of the suture.

**Lithiasis:** Recurrent urinary infections may be a sign of urethral stones. Its formation is frequent when large areas of urethra are reduced with urinary stasis develop. In the case of having used flaps, the presence of hair may have produced a precipitation of secretions, and formation of lithiasis.

**Urethral diverticula:** In the case that the pedunculated grafts are too wide or redundant, pseudo-diverticula can be formed. The patient may complain of postvoid drip, urethral bulging during urination, or the presence of recurrent urinary infections. The treatment of a postsurgical urethral diverticulum is the exeresis of the redundant tissue, the correction of distal obstructions, and the molding of the urethra to an adequate caliber.

**Incontinence:** In patients with posterior urethral strictures secondary to pelvic fractures, the cause may be difficult to determine.

**Incurvation and erectile dysfunction**: Erectile dysfunction tends to be transient when it does occur and recovers in the majority by 1 year. Trend for worse outcome with anastomotic bulbar

procedures compared to bulbar grafts and non-transecting techniques. In a journal article written by Coursey *et al.,* 200 men who underwent anterior urethroplasty answered a questionnaire to evaluate postoperative sexual function. Does who undergo BMG urethroplasty had a 19.2% worsened the satisfaction with erection, 30.8% had a mild change in the erectile angle, and 7.7% a major change, while 15.4% had a major change in the erect length. In conclusion, most of the alterations when undergoing an anterior urethroplasty appear to be transient or associated with a longer stricture (2,35).

# JUSTIFICATION

A urethral stricture is a decrease in the size of the urethra, usually caused by scar tissue impairing urinary flow. The majority of the narrowing of the urethra develops only later in life, affecting mainly men, and especially the anterior part of the urethra called bulbous.

In a large number of patients, the cause is unknown, while other common causes for acquired urethral strictures are bacterial infections, injuries in the pelvis, urethral interventions, or tumors of the urethra.

Urethral strictures are the result of a gradual pathogenesis, so the symptoms tend to appear gradually and are often not noticed until the pathology is really advanced. Some of the lower tract urinary symptoms a patient may refer are not specific such as weak urinary stream or incontinence, burning sensation during urination, incomplete bladder voiding, inability to urinate, frequent urge to urinate, hematuria, etc. There is an increasing resistance while urination, it can lead to UTI, and bladder distension as well as diverticula in the bladder wall.

The diagnose is based on medical history, physical examination, and an uroflowmetry. Other techniques such as RUG, and VCUG are used. In addition, ultrasound examination is performed. After these examinations, a urethral endoscopy can be proceeded.

When the urethral stricture is less than 4 cm, different techniques may be used, such as dilators, DVIU, and EPA or augmented EPA. The urethrotomy is only an intermediate solution, not an appropriate treatment option. Urethral reconstruction and repair with native oral mucosal tissue is the method for treating urethral strictures.

During the last decades different techniques employed have been modified and improved. The most recent development in urethra surgery is how use of oral mucosa has become established. In contrast with many other tissues, oral mucosa is perfectly suited for substituting for urethra loss, for replacing sections of the urethra and in particular for expanding constricted urethras.

Commonly, a strip of oral mucosa is removed from inside the cheek and then directly transplanted to the urethra. One of the disadvantages of this procedure, however, is that a large piece of oral mucosa has to be removed from the mouth, producing some local disadvantages for the patient.

Even though some patients with harvesting buccal mucosa from a single cheek will provide enough tissue for the reconstruction, sometimes more tissue is required, and the contralateral cheek, lingual mucosa or labia mucosa can also be used. Therefore, more extensive grafting

increases the risk of donor site morbidity. The main complications can include salivary duct and nerve damage, and after there can be pain, numbness, bleeding, infection and swelling, there can be scarring and contraction which leads to tightness affecting jaw opening and speaking disorders.

Another complication of buccal mucosa graft harvesting is the limitations of its availability in patients that may present recurrent strictures, or in patients who have limited jaw opening or maxillofacial disorders. As well as the limitation of buccal mucosa in those panurethral strictures, where large pieces of buccal mucosa graft are needed. The use of buccal mucosa implies, unlike the skin of the penis, involves the creation of another surgical field, which lengthens the procedure.

The MukoCell® innovation does not require the removal of large pieces of oral mucosa, instead only a small sample of the mucosa is taken, and for 3 weeks, in a special lab, oral mucosa is applied to a carrier matrix.

This mucosa can be produced at any quantity required which means, it is going to be able to reconstruct even longer urethra defects easily. The use of MukoCell® helps avoid the need to remove large sections of mucosa from the mouth, as well as the number of complications.

The technique is relatively easily, and the operation time is significantly reduced, the patient's quality of life is significantly better, as all oral complications can be avoided. As the technique is more rapidly done, the time of the operation is reduced, reducing the time of lithotomy position of the patient, and the problems that this entails.

This treatment would imply an innovative improvement in the treatment of the anterior urethral strictures, which would reduce the complication of the oral harvest and the treatment in the urethra itself, as well as the symptoms due to stricture urethra.

Therefore, the intention of this study is to undergo a prospective, randomized, open-label, clinical trial to compare and evaluate the results and improvement in different functional tests, the reduction of short-term complications and long-term complications, the number of days of hospitalization, and the improvement of quality in life in patients who, after a urethroplasty with MukoCell®, and in those who received the BMG urethroplasty. This study pretends to know if our hypothesis is true, and therefore, provide enough evidence to validate the new minimally invasive technique.

# HYPOTHESIS

## GENERAL HYPOTHESIS

In the adult patients that present a urethral stricture the use of MukoCell® technique has better post-intervention outcomes and improvement in the different functional tests compared to the use of buccal mucosa urethroplasty; in the sense that MukoCell® technique reduces short-term and long-term complications, as well as the number of days of hospitalization, improving at the same time the quality of life of the patient, and the presence of buccal mucosa complications.

# OBJECTIVES

## GENERAL OBJECTIVE

The primary aim of this study is to register and compare the post-intervention outcomes using different functional tests in patients with urethral stricture after having buccal mucosa urethroplasty in comparison to those who received MukoCell® technique.

## SPECIFIC OBJECTIVES

- Compare short-term complications in patients with urethral stricture using both techniques.
- Compare long-term complications in patients with urethral stricture using both techniques.
- Compare buccal mucosa complications in patients with urethral stricture using both techniques.
- Register and compare the number of days of hospitalization in both techniques.
- Compare the improvement in the quality of life in both techniques.

# MATERIAL AND METHODS

## 1. STUDY DESIGN

A prospective randomized, controlled and open-label clinical trial is proposed to compare and evaluate the improvement on clinical and objective examinations, the amounts of days of hospitalization, and complications related to the procedure in patients who presented a urethral bulbar stricture, with a length superior to 2,5 cm, and underwent a urethroplasty using a BMG (control group), and those who received the graft using the MukoCell® technique (intervention group).

We understand as objective examinations: uroflowmetry parameters, retrograde-voiding (RUG-VCUG) urethroscopy and post-void residue.

The main complications related to the procedure are bleeding, restenosis and erectile dysfunction.

Patients will be randomly assigned into 2 groups with a ratio 1:1. The first one, the intervention group, will be undergoing a urethroplasty using the MukoCell® technique for grafting, while the control group will be receiving a buccal mucosa graft.

The study will be performed entirely in HUDJT.

## 2. STUDY POPULATION

The populations of this study will be 18 years or older people that is resident in the Girona Health Region (includes the province of Girona except Cerdanya and has as a reference the HUDJT), that are males diagnosed of bulbar stricture urethra, and will be needing urethroplasty using grafts for its treatment.

All patients must meet the inclusion and exclusion criteria.

### 2.1. INCLUSION CRITERIA

- Patients aged 18 years old or over.
- Male patients.
- Patients diagnosed with bulbar urethra stricture larger than 2.5 cm by a urethrogram.

- Patients who present either symptoms or altered functional test such as uroflowmetry, with a maximum urinary flow rate (Qmax) less than 15 mls/min.
- Patients who have signed the informed consent and who have read the information sheet for participants (Annex 9 and 10)

### 2.2. EXCLUSION CRITERIA

- Patients that received radiation therapy and radical prostatectomy for prostate cancer.
- Patients with restenosis of the urethra.
- Patients in which one of the techniques for urethral strictures have failed before.
- Patients with previous hypospadias treatment.
- Patients with any of the relative and absolute contraindications for BMG harvest.
- Patients who cannot undergo complete anesthesiology or present contraindications.
- Patients who are not able to understand the surgical procedure that will be performed.

### 2.3. PARTICIPANT WITHDRAWAL OR TERMINATION

All participants in the study are free to decide at any time upon request to withdraw the study.

When they decide to withdraw the study, participants must communicate their decision to the research team, or one of the physicians responsible for the study.

A patient will be considered not to want to take part in the study, after several attempts to contact him/her, if he/she does not answer two of the calls to attend the follow-up or is considered to have lost the follow-up of the intervention.

Patients who present exclusion criteria, either newly developed or not recognized at first, will also be considered to have dropped out of the study.

In case of withdrawal or death, no extra patients will be added to the clinical trial, since all patients who are part of the study are already included in the statistical analysis.

# 3. SAMPLE

## 3.1. SAMPLE SIZE

Computations were carried out using the GRANMO program.

Accepting an alpha risk of 0,05 and a beta risk of 0,2 in a two-sided test, 66 patients are needed in the first group and 66 patients in the second group to detect a statistically significance difference between the two proportions. A proportion difference expected to be 0,90 in the first group 1 and 0,70 in group 2. It has been anticipated a drop-out rate of 10%. The ARCINUS approximation has been used.

- Group 1 (intervention group, using MukoCell® technique graft) with an anticipated prevalence of 90% better outcome.
- Group 2 (control group, urethroplasty using BMG) with an anticipated prevalence of 70% outcome.

If we take in account the number of patients that undergo the procedure of the urethroplasty in a year, we can see that it is possible to get all the patients in five years and 6 months, and to analyze the data collection during the following year.

## 3.2. SAMPLING

As patients will be presented as they get diagnosed by specialist, they will be asked if they are interested in joining the clinical trial.

This is a non-probabilistic consecutive sampling.

## 3.3. SAMPLE SELECTION

Starting this trial, in June 2021, the urologist working in our hospitals must elect by order of arrival a total of 132 patients. Considering that every year, an estimation of 25 new cases are diagnosed in our hospital network, meeting the inclusion criteria we deduce that 5 years and 6 months are needed to fulfill our requirements.

# 4. VARIABLES

Patients will be taken their patient history and will be asked to complete some questionnaires from the European Association of Urology (EAU) and to do urine analyses, cystourethroscopy, cystourethrography, and flow measurements on the 8th day post intervention, and in 6, 12, and 24 months consecutively.

## 4.1. INDEPENDENT VARIABLES

The independent variable of this study is the intervention performed for urethral stricture treatment, that is, whether our patients receive the urethroplasty using BMG or the MukoCell® graft.

This a dichotomic qualitative variable.

## 4.2. DEPENDENT VARIABLES

**Presence of prostatic symptoms**

During the anamnesis, we must identify the different lower urinary tract symptoms (LUTS), and their severity, which determines the quality of life of the patient, and the individualized therapeutic techniques used in each case. The LUTS can be divided in:

- Obstructive (mechanical): initial difficulty, weak jet, post-void grip, intermittent urination, and incomplete emptying.
- Irritating (dynamics): frequency, nocturia, urination urgency, urge incontinence, and suprapubic pain.

This is an ordinal qualitative variable. The measure method is the IPPS.

The IPPS is a validated questionnaire (Annex 4) used to evaluate the gravity of the lower urinary tract symptoms, associated with different diseases in men, in this case with the presence of a urethral stricture. It is formed by eight questions. The first 7 are about symptoms in the patient, and the last one about the quality of life. With the results, we can differentiate between mild, moderate or severe symptoms.

An improvement in the symptoms score from the baseline measurement of at least 3 points, is considered as perceptible, and therefore, as a minimum threshold for clinical improvement.

**Urodynamic measures**

The urodynamic measures are a binary qualitative variable, which can be pathological or non-pathological.

The measure method used is the uroflowmetry. An uroflowmetry is a test performed in urology in patients presenting voiding symptoms, as much as problems urinating.

It is defined as the amount of voiding volume (urine) eliminated per unit of time. It its expressed in cm3 or ml per second. The voiding flow is not constant, so the different flow curves are measured as well. The amount of urine in the bladder capable of urinating per second, the durations of urination, and the amount of intermittent flow are measured. The residue is also measured, that is, the amount of urine that remains in the bladder after urinating.

The parameters that we are going to measure are:

- Maximum flow: maximum value reached by urinary flow during urination. We consider that a peak flow less than 10 ml can tell us the presence of obstruction.
- Voiding volume: amount of urine eliminated in urination.
- Flow time: is the sum of all the time during which the patient voids.
- Urination time: time that elapses between when the patient starts urination until it ends.
- Mean flow: result of dividing the voiding volume by the flow time.
- Post-voiding residue: quantity of urine that remains in the bladder after finishing for complete the urination. Values above 20-30% of total volume is considered pathological.

This test shall be repeated if the urination volume is below 150 cm3, or the patient made an extra-effort with the abdomen.

Another urodynamic measure will be the use of the RUG-VCUG. The current gold standard is the RUG, in complex situations it can be combined with a VCUG. It is a dichotomous nominal qualitative variable, in which the expert can assess the images and tell us if there is a presence or not of any abnormalities.

**Health-related quality of life and patient satisfaction**

This is an ordinal/binary qualitative variable.

The measure method is the USS-PROM questionnaire (Annex 3). In patients undergoing anterior urethral surgery the valid instrument for quantifying changes is the USS-PROM questionnaire. The questionnaire should be completed before and after the surgery. The questionnaire was developed for early identification of the patients at risk of developing symptoms and complications of urethral stricture, and also good instrument for assessing need to intervention.

It consists of 4 main constructs: lower urinary tract symptoms, and LUTS-related, quality-of-life (QoL) domain, Peeling's voiding picture, EuroQoL dimensional scale (EQ-5D), and post-operative overall patient satisfaction questions.

In the first domain each question is scored from 0 to 5, which gives a total score from 5 points (least or no symptoms) to 35 points (most symptoms), we consider from 6-9 mild symptoms, from 10-20 moderate, and from 21-30 severe symptoms. In the second domain, is a question relating LUTS to the quality of life, and a visual scale to assess the urine stream using the Peeling's voiding picture.

The third domain contains five questions about overall health status and quality life, from the EuroQoL-5D questionnaire.

The last domain are two questions about patient satisfaction with the results of the operation.

**Complications:**

Up to 50% of the patients may present spraying of urine. Less common complications include erectile dysfunction, wound infection, urinary fistula and anastomotic leak. Stricture recurrence can be another complication, mainly detected after long-terms follow-up (>10 years). There are no gold-standard for post-operative screening protocols but recommend a combination of patient symptom assessment, noninvasive test such uroflowmetry, cystoscope and RUG/VCUG.

The Clavien-Dindo classification (Annex 6) qualifies the type and mode of any type of treatment applied to each complication. It can be modified based upon objective data, decreasing the subjective interpretation.

- **Infection of the wound**

Considered an ordinal qualitative variable. We can classify the infection of the wound based on the continuum stages:

  - Contamination and colonization: there is no presence of wound signs infection.

- Local infection: erythema, local warmth, swelling, purulent discharge, delayed healing, increase of the pain, increasing malodor.
- Spreading infection: in which we have wound and systemic signs and symptoms like increased and extended erythema, lymphangitis, crepitus, wound breakdown/dehiscence, patients feel unwell, inflammation, or enlarged lymph nodes.
- Systemic infection: systemic inflammatory response, sepsis/severe sepsis, septic shock, organ dysfunction, death.

- **Infection / Urethritis**

Inflammation of the urethra is most commonly caused by UTI and can present with dysuria, discharge and irritation to penile tip, testicular tenderness and inguinal lymphadenopathy. So, it is going to be considered a dichotomic nominal qualitative variable (Yes/No).

- **Bleeding**

This is an ordinal qualitative variable. The bleeding as a complication can be classified in different grades:

- 0: Absent
- 1: Petechiae
- 2: Ecchymoses and/or dripping with moderate loos of blood
- 3: Major mucous hemorrhage with copious loss of blood without sequelae.
- 4: Major mucous and/or parenchymal hemorrhage with copious loss of blood with sequalae and/or life threatening or death.

- **Restenosis**

When being asymptomatic with normal flow rate, the only way to detect a possible restenosis is with a urethroscopy, when the flow rate diminishes it means the urethral caliber is <11 Fr, and the recurrence can be detected with a uroflowmetry, if it continues progressing there is going to be a recurrence of the symptoms. The restenosis is a dichotomic nominal qualitative variable, answering Yes/No, to the presence of it.

- **Fistula**

Some inappropriate surgical procedures can lead to the incomplete wound healing, forming a urethra-cutaneous fistula. When performing RUG-VCUG, a leakage can be visualized. The fistula is a dichotomic nominal qualitative variable, answering Yes/No, to the presence of it.

- **Urethral diverticula**

It is the development of a sacculation, they can be filled with urine and lead to infections. Imaging tests can be used to find UD. The urethral diverticula is a dichotomic nominal qualitative variable, answering Yes/No, to the presence of it.

- **Erectile Dysfunction**

The ED is the inability to get or keep an erection firm enough to have sexual intercourse. It is an ordinary qualitative variable.

The erectile dysfunction can be classified depending on the degree of rigidity achieved in the erection and the interference it produced with the patient's sexual activity. To evaluate the erectile dysfunction the IIEF-5 test is used. This is an ordinal qualitative variable.

The IIEF-5 questionnaire (Annex 5) is a validated, multi-dimensional, self-administered investigation that has been found useful in the clinical assessment of erectile dysfunction, as well as treatment outcomes.

The following table shows us the criteria needed to consider the MukoCell® urethroplasty as a favorable outcome. In the case that all the items in the favorable outcomes' column are presented, we consider the technique as satisfactory, whereas if there is the presence of an item in the unsuccessful outcomes' column, we consider it an unsuccessful technique.

*Table 6. Summary of instruments and measures used to assess the better post-outcome in MukoCell®*

| TESTS | | FAVORABLE OUTCOMES | UNSUCCESFUL OUTCOMES |
|---|---|---|---|
| **IPPS (Symptoms)** | | Non presence/ Mild | Moderate/Severe |
| **USS-PROM** | Symptoms | <5 (normal) | ≥5 |
| | Quality of life | Good | Bad |
| **Uroflowmetry** | | Peak flow ≥10 ml | Peak flow <10 ml |
| **RUG-VCUG** | | Images assess of normality | Presence of abnormality |
| **Urethroplasty complications** | | Absence of complications | Presence of any complication |
| **IIEF-5** | | No ED/Mild ED | Mild-moderate/Moderate/Severe |

**Buccal mucosa complications**

The more common postoperative complications of urethroplasty include swelling and bruising around the wound, numbness, or discomfort around the buccal mucosal graft donor site.

It is a dichotomous nominal qualitative variable. And it will be answered as Yes/No question.

We include as complications:

- Swelling and scarring
- Injuries to the salivary glands' orifices
- Problems with the intake of food or liquids
- Restriction of the opening of the mouth.

**Days of hospitalization**

A urethroplasty is considered a shorter duration procedure, usually patients who undergo this procedure, the hospital stays of two- or three-days duration are the average.

This is a discrete quantitative variable, in which we measure the number of days of hospitalization after undergoing urethroplasty.

### 4.3. COVARIATES

Baseline data will be collected during the first interview with the patient and the clinical history of the patients, a week before the procedure, after signing the informed consent form.

These characteristics might potentially influence on the relation between the independent and the dependent variables, acting as a confounder variable, so covariates are going to be contemplated and it will be necessary to stratify the patients according to these, to see if they influence on the result.

- Age: it is discrete quantitative variable. It will be expressed in years.
- Marital status: it is a nominal qualitative variable. It is going to be measured as Single/Divorced/Widow/Married/Living in couple
- Body Mass Index (BMI): It is a categorical quantitative variable. It is important, as a high BMI is related with wound dehiscence, wound infection, ulcers, and hematoma (Annex 7).
- Smoking: it is qualitative dichotomic variable. Smoking is a variable related to wound rupture, infection, and graft necrosis, and also anastomotic leakage. It will be measured as a Yes/No question.
- Previous stricture treatment: it is a dichotomous nominal qualitative variable (Yes/No).
- Time between the diagnosis until the first intervention: It is a discrete quantitative variable, expressed in months.
- Comorbidities: presence of external mass, tumors or diseases like BPE, which can be presented with the same LUTS. The presence of diseases, such as diabetes mellitus or cardiovascular diseases which are both risk factors. It is a dichotomous nominal qualitative variable (Yes/No)

*Table 7. Independent and dependent variables*

| | Variable | | Description | Measurement |
|---|---|---|---|---|
| **Independent variable** | Urethroplasty using MukoCell® | | Dichotomic qualitative | Use of intervention (Yes/no) |
| **Dependent variable** | Prostatic symptoms (LUTS) | | Ordinal qualitative | IPPS Questionnaire |
| | Urodynamics | | Dichotomic nominal qualitative | Uroflowmetry, RUG-VCUG (Presence of abnormalities) |
| | Quality of life and patient satisfaction | | Ordinal qualitative variable | USS-PROM Questionnaire |
| **Secondary dependent variables** | Short-term complications | Infection wound | Ordinal qualitative | Continuum stages |
| | | Urethritis | Dichotomic nominal qualitative | Presence of symptoms |
| | | Bleeding | Ordinal qualitative | Different grades |
| | Long-term complications | Restenosis | Dichotomic qualitative | Presence of restenosis (Yes/No) |
| | | Fistula | Dichotomic qualitative | Presence of restenosis (Yes/No) |
| | | Urethral diverticula | Dichotomic qualitative | Presence of restenosis (Yes/No) |
| | | Erectile dysfunction | Ordinal qualitative | IEEF-5 Questionnaire |
| | Days of hospitalization | | Discrete quantitative | Number of days |
| | Buccal mucosa complications | | Dichotomic nominal qualitative | Presence of complications (Yes/No) |

*Table 8. Covariables*

| | Variable | Description | Measurement |
|---|---|---|---|
| Covariables | Age | Discrete quantitative | Years |
| | Marital status | Nominal qualitative | Single, divorced, widow, married, living in couple |
| | Body Mass Index | Categorical quantitative | BMI |
| | Smoking | Dichotomic qualitative | Yes/No question |
| | Previous stricture treatment | Dichotomic nominal qualitative | Yes/No question |
| | Time between the diagnosis until intervention | Discrete quantitative | Months |
| | Comorbidities | Dichotomic nominal qualitative | Yes/No question |

# 5. INFORMATION AND DATA COLLECTION

Information will be collected from the different clinical interviews and medical history, in 5 different times:

- Before being admitted for surgery
- After the urethroplasty → the 8th day post-urethroplasty
- 6 months after discharge
- 12 months after discharge
- 2 years after undergoing urethroplasty

Both checks-up will be done by a blinded specialist, to blind the study. All the information and data will be collected in a database created specifically for this clinical trial with the Excel software.

Covariables will be collected from the patient's medical history during the first visit.

Patients needing an anterior urethroplasty using buccal grafts, will be evaluated at the urologist practice, to see if they meet the inclusion and exclusion criteria.

The information concerning this study and invitation to participate must be handled to the patient, before entering the trial. The acceptance will only be valid if the individual signs an informed consent.

After consent is given, a code will be assigned to each patient to decide which treatment will be applied. It is important to understand that they can be assigned to any of the 2 techniques, and they must agree with the result.

## 5.1. TRIAL ENTRY

To confirm that the patients are suitable for the trial, the team of urologists that participate in the trial will do themselves an anamnesis, a physical examination, and will proceed to do the complementary tests needed to verify the absence of exclusion criteria.

The complementary tests will be a uroflowmetry, a RUG-VCUG, as well as the different questionnaires for testing the dependent variables, such as the IPPS, USS-PROM, and IIEF-5.

The remaining patients after undergoing the different tests and clinical history will be randomized into two groups. The randomization will be stratified according the covariables.

### 5.2. ANESTHESIOLOGIST VISIT

Before the surgical procedure, the patients will visit the anesthesiologist, who will decide if the patient can be operated, and the operatory risk the patient presents, with the American Society of Anesthesiologist Physical Status (ASA PS) classification system (Annex 8).

### 5.3. INTERVENTION DAY

Depending on the group assigned to the patient, a urethroplasty using BMG will be done (control group), or a urethroplasty using the MukoCell® technique (intervention group).

In those patients with buccal mucosa grafting, the urethroplasty will be proceeded at the same time as the buccal harvest is done, in a two-team approach.

In intervention group patients, a buccal biopsy will be taken in a pre-intervention day, and the sample will be cultured in the given scaffold by the manufacturer, following its' instructions, and afterwards sent to the MukoCell® GMP laboratory, to grow the autologous sample, and obtain the new tissue-engineered graft. These patients will be cited 3 weeks after this intervention, to undergo the major intervention, which is the urethroplasty.

During the stay at the hospital, which has an average stay of 2-3 days, the patients will undergo different physical exams, to see the evolution of the wounds, as well as the classic control in these kind of patients.

### 5.4. FOLLOW-UP

The first post-operative encounter will be on the 8$^{th}$ day, to take out the urethral catheter, and proceed with a clinical anamnesis, a VCUG, and so the patients can answer the different questionnaires.

Patients will be followed-up for 6 months after the intervention, and the next follow-up visits will be scheduled after 12 and 24 months, by assistants who will be unaware of which intervention the patients received. However, if any complication appears after the intervention the patient is informed to come back as soon as possible.

During the follow-up visits patients will undergo an anamnesis, a physical exam, different functional test such as uroflowmetry and RUG-VCUG. Patients will also have to answer the different questionnaires, that were presented before the surgery, which includes the IPPS, USS-PROM, and the IIEF-5.

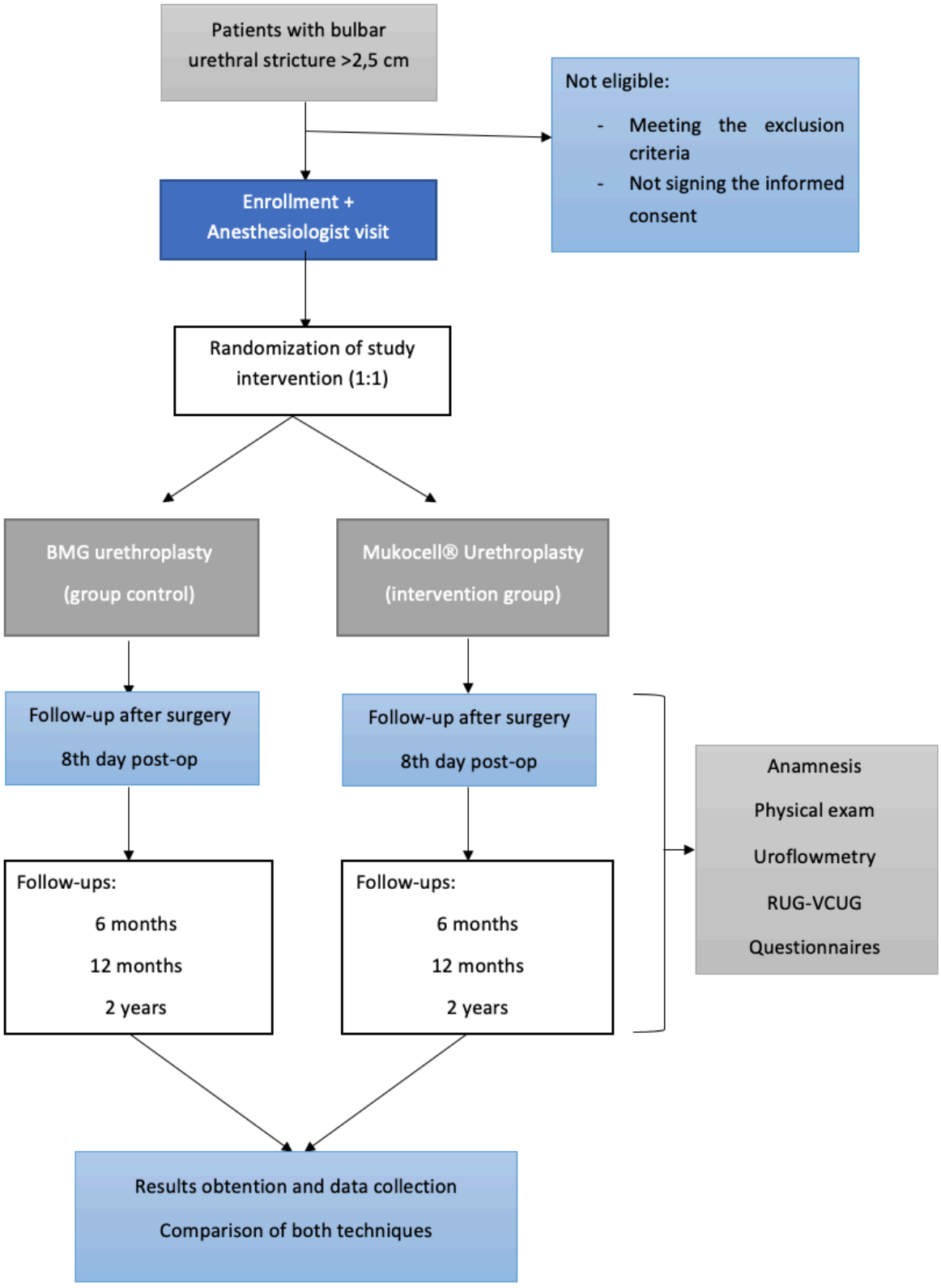


*Figure 9. Flow chart*

## 6. SAFETY

The technique used as a group control in this clinical trial is a urethroplasty using buccal mucosa grafts, as this technique has already been applied, the systematic reviews show safety for the procedure.

The MukoCell® product for urethroplasty has already been applied and has demonstrated the safety of the procedure, since it is a product manufactured in a GMP laboratory.

Both short-term and long -term complications have been taken into account in this clinical trial.

In the short-term we include wound infection, urethritis, and bleeding. While in the long term, restenosis, fistulas, lithiasis, urethral diverticula, incontinence, and erectile dysfunction may occur.

## 7. SATISTICAL ANALYSIS

The statistical analysis will be performed by a statistical analyst, blinded to the study groups, with the Statistical Package for social Sciences (SPPS) software version 25 (IBM, Armonk, NY, US) for Windows ®.

In all cases, a confidence of 95% will be assumed and $p<0.05$ will be considered statistically significant. P meaning the changes of the result being by chance.

### 7.1. DESCRIPTIVE ANALYSIS

The lower urinary tract symptoms, urodynamic measures and complications (erectile dysfunction, buccal mucosa complications) will be summarized through proportions, stratified by the intervention and the control group.

In the univariate analysis, variables will be defined as quantitative or qualitative:

- For quantitative variables and covariables we will use measures of central tendency and dispersion measures.
- For qualitative variables and covariables, we can express it with percentages or proportions, and confidence intervals.

### 7.2. BIVARIATE INFERENCE

The association between the decrease of LUTS, urodynamic measures, and complications (erectile dysfunction, buccal mucosa complications) and the independent variable, will be contrasted using the Chi-Square test.

These analyses will be stratified by the covariates. When covariates are quantitative, the T-Student test will be used.

In summary for the evaluation of quantitative variables, using averages, the T-Student test will be used. When comparing qualitative variables, the percentages and to analyze measures, the Chi-square test will be used.

### 7.3. MULTIVARIATE ANALYSIS

A multivariate analysis will be carried out to adjust variables for covariates, trying to avoid confounders that could modify the result of the study.

Covariates contemplated in this study are age, marital status, BMI, smoking, previous stricture treatment, time between diagnosis and treatment and comorbidities.

It is important to remember that patients have been randomized so the groups should be balance out.

To assess the effects on post-intervention outcomes (dependent variable) when using the MukoCell® technique compared to the BMG urethroplasty (independent variable) we can use logistical regression adjusting with each co-variable.

We can also stratify each result adjusting to each covariable in each group to learn more about our statistics.

# WORK PLAN AND CHRONOGRAM

The whole study will take approximately 8 years and 9 months. It will be divided in the following phases.

**PHASE 0: Study design (3 months)**

The protocol of the study will be designed by the main investigator (MI). This protocol will contain a detailed explanation of the variable and objectives proposed for the study.

Protocol will be given to the Ethics Committee (CEIC) of HUDJT for its revision and approval, and the hospital itself. All suggested changes will be taken into account.

Subsequently, after the CEIC approval, the authorization of the EMA and the AMEPS as well will be expected to carry out the clinical trial. As the product is already in EMA approval, the authorization and approval of MukoCell® as a medical product would be needed by the AEMPS.

As well as the recruitment of a coordinator for the study in the center involved.

**PHASE I: Preparation and coordination (2 months)**

After CEIC and AEMPS approval, a work chronogram will be prepared with all the phases detailed, procedures, and a general coordination meeting will be held. This meeting includes urologists' specialists, nursing staff, radiological staff, lab staff, administrative staff, statistics and every person that has a role in the study. This meeting aims to explain and discuss the design, objectives and methods of the trial, and any other information regarding the study. All the participant professionals will be trained on what they have to request and how to collect information.

The UroTech laboratory will also be contacted in order to obtain the product.

It is important to ensure that everyone who participates in this study knows their task and how to carry it out.

**PHASE II: Field work and data collection (7 years and 6 months)**

Sample recruitment will take 5 years and a half. All the patients presenting urethral bulbar stricture who meet the inclusion and exclusion criteria, recruited by a consecutive method, will

be informed about the study and invited to participate voluntarily if they are interested, before undergoing the urethroplasty.

All patients will be given a written explanation document with the details of the interventions.

If the patient agrees to participate in, along with the patient's medical history and the information he will give us, all data needed for the study will be collected.

Patients are going to be randomly placed in one of the two groups of the treatment.

Patients who are assigned to the control group will have a urethroplasty performed using the buccal mucosa graft (BMG), and patients who are assigned to the intervention group will have a urethroplasty performed using the MukoCell® technique.

All the patients will be followed-up for two years after the treatment.

Since we are going to be recruiting patients for a long period of time, the data will be collected as the patients are operated on by the blinded statistician. A meeting will be held when we obtained the results for half of the sample we analyze, i.e., approximately 33 patients in each research group, in order to obtain preliminary results. This way we will be able to have some results, and to see the evolution of our clinical trial, how it evolves and take into account the main characteristics and variables of the clinical trial, to ensure it is being done correctly.

**PHASE III: Data analysis and interpretation (4 months)**

Once data collection is completed and collected, it will be classified and organized, so a blinded statistician will present the results to all the research team.

A final meeting will be held to present and discuss the results by the research team to take care of the analysis and interpretation of the data.

**Phase IV: Results publication (6 months)**

The MI will be the person in charge to elaborate the final article. It will be published in a Urology journal in order to properly distribute the results of the study. Moreover, the results will be exhibited in national and international congress of specialists.

The team needed for this trial study is:

- Main investigator (MI): it is the person responsible for elaborating the projects protocols, assembling the team and making sure that everything needed for the project is ready.
- Clinical coordinator: in our hospital center, the coordinator makes sure that the clinical trial is done the way it is specified. The main coordinator communicates with the MI if there are any doubts or other situations.
- Urologist professionals: They will be aware of the project and participate when they can to help implement the measures as controlled as possible.
- Other personnel: this is will be some personnel hired for the study, such as a statistical analyst, that will evaluate the data from patients' results.

| Years | 2021 | | | | | | 2022-2026 | 2027-2028 | 2029 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Months** | FEB | MAR | APR | MAY | JUN | JUL-DEC | JAN-DEC | JAN-DEC | JAN- FEB | MAR-APR | MAY-JUN | JUL-AUG | SEP-OCT |
| **PHASE 0: STUDY DESIGN** | | | | | | | | | | | | | |
| **Protocol elaboration** | | | | | | | | | | | | | |
| **Protocol approbation (CEIC, AEMPS)** | | | | | | | | | | | | | |
| **PHASE I: PREPARATION AND COORDINATION** | | | | | | | | | | | | | |
| **Chronogram elaboration** | | | | | | | | | | | | | |
| **Coordination of research team and meetings** | | | | | | | | | | | | | |
| **PHASE II: FIELD WORK AND DATA COLLECTION** | | | | | | | | | | | | | |
| **Patient recruitment** | | | | | | | | | | | | | |
| **Intervention** | | | | | | | | | | | | | |
| **Data collection** | | | | | | | * | | | | | | |
| **Follow-up** | | | | | | | | | | | | | |
| **PHASE III: DATA ANALYSIS AND INTERPRETATION** | | | | | | | | | | | | | |
| **Statistical analysis** | | | | | | | | | | | | | |
| **Interpretation** | | | | | | | | | | | | | |
| **PHASE IV: RESULTS PUBLICATION** | | | | | | | | | | | | | |
| **Final Article elaboration** | | | | | | | | | | | | | |
| **Result publication** | | | | | | | | | | | | | |
| **Dissemination** | | | | | | | | | | | | | |

*Meeting staff to evaluate the data collection obtained

*Figure 10. Work Chronogram*

# BUDGET

All research team and personnel are employees of the Hospital, so it will not be necessary to hire any workers for clinical functions.

Apart from that, the BMG urethroplasty is part of the normal procedure used in the clinical practice, as well as the follow-up of our patients.

The insertion of a catheter and complications also form part of the routine activity related to these patients and will not suppose an extra cost.

**Extra services**

A statistician will be needed in order to create a data base, randomize the patients, and perform the statistical analysis. It is expected that 80 hours will be needed, and the salary of our statistician is 25 €/hour, so this will cost a total of 2.000 €.

In addition to the statistical analyses, a clinical researcher associated who will be responsible of data monitoring and control is also needed, to give assessment and coordinate the medical staff involved and the patients. 1 hour per week is necessary, adding up a total of 104 hours. This will mean 2600€ in a salary of 25€/hour.

**Material**

To go on with this study some extra material is needed for the intervention group. And will be used for every patient in the intervention group. Each unit of MukoCell® has an approximate cost of 3.600€, due to the need to fulfil the requirements of the EMA in order to obtain the marketing authorization. As we have a total number of 66 patients, undergoing MukoCell® technique, it would cost a total of 237.600€.

Due to the expenses of the material itself a series of grants and funding have been sought in order to reduce the final cost. Some of the ones we see feasible when applying are those related to urological research, such as the 3 grants aimed at members of the Spanish Association of Urology for the funding of cooperative research projects in the field of urology.

The information sheet, informed consent, and all printed papers will be taken into account. It will be needed to invest 1€ for each patient, so a total of 132€ will be needed for printing and papers.

**Insurance**

An invasive procedure is performed, so it is necessary to hire an insurance for the patients, with a total of 100€ for each patient, with a total cost of 13.200 €.

**Publication and dissemination**

The approximate cost for the publication of the results will be 2300€ (500€ for the English correction and 1800€ related to the publishing cost of an Open Access article).

*Table 9. Budget*

| | TYPE of COST | COST | AMOUNT | SUBTOTAL |
|---|---|---|---|---|
| **SATFF COST** | Expert statistician | 25€/h | 80 h | 2.000€ |
| | Clinical Research Associate | 25€/h | 104 h | 2.600€ |
| **MATERIAL** | MukoCell® | 3.600€ | 66 | 237.600€ |
| | Printing and papers | 1€ | 132 | 132€ |
| **INSURANCE** | Insurance covering damage | 100€ | 132 | 13.200€ |
| **PUBLICATION AND DISSEMINATION** | English correction | 500€ | 1 | 500€ |
| | Publishing costs | 1.800€ | 1 | 1.800€ |
| **TOTAL COST** | | | | **257.832€** |

# LEGAL AND ETHICAL CONSIDERATIONS

This study will be conducted according to the human rights and ethical principles established and defined on the World Medical Association in the Declaration of Helsinki of Ethical Principle for Medical Research Involving Human Subjects. The research protocol of our study must be presented, evaluated and approved by the Clinical Research Ethical Committee (CEIC) at HUDJT. All the recommendations will be considered, and relevant modifications will be made to get its approval. This process will be followed at the beginning and at the end of the study.

Personal and clinical information and other data collected for the study of all participants will be confidential and only used for research according to *"Ley Orgánica 3/2018, de 5 de Diciembre, de Protección de Datos Personales y garantía de los derechos digitales"*.

An information sheet with all the important aspects of the study will be given to each participant (Annex 9), where all risks, benefits and alternatives to the procedures will be detailed using the best updated data available at that point, to ensure they perfectly understand the study before they sign the informed consent to entry the study (Annex 10).

The clinical trial will be performed following the *"Ley 14/2007, de 3 de Julio, de Investigación biomédica relacionada con procedimientos invasivos, muestras biológicas y biobancos*" in which an invasive procedure is defined as an intervention performed with research objectives involving physical or psychological risk for the affected subject, as well as the "*Real Decreto 1090/2015, investigaciones clínicas con productos sanitarios".*

Exclusion criteria has been stablished respecting the principles of justice and beneficence, since most patients can be part of the study, and doctors and other medical workers who take part in it are accredited and well trained for their assigned tasks, so the principle of non-maleficence will be respected.

The research team will assert that all the results will be published with transparency and clarity.

All investigators involving the study will have to declare no conflict of interest.

# STRENGHTS AND LIMITATIONS

Analyzing this study, some limitations that may interfere to the research have been detected and taken into consideration:

- We may present a selection bias, due to the consecutive recruitment proposed, which in this study is a non-probabilistic recruitment and may not obtain the best representative sample. Moreover, due to the high prevalence among aged males, presenting urethral strictures the sample may be biased. This means a low number of young male patients will be expected.

  Nevertheless, to minimize this bias, a number of exclusion criteria have been set as well as randomization has been performed, to help distribute symmetrically the covariates to be able to extrapolate future results on the general population.

  A selection bias can be also caused by losses and withdrawals as well, which is why in the estimation of the sample size, a drop-out of 10% has already taken into account.
- Not all patients will be able to receive general anesthesia, due to some comorbidities, which is a limitation for the study. These losses, even though they are not expected, they will be counted as withdrawal, after going through the anesthesiologist visit.
- An additional limitation of this study is related to the open-label design. Studies applying surgical techniques have a detection bias because of the unfeasibility of blinding the surgeon, and in this study, it is also not possible to blind the patients.

  To minimize this bias, the study will be an examiner-blind trial. The follow-up visits are going to be done by an assistant who will be unaware of which treatment group the patients had been assigned to. During the examination, there will not be any sign that can reveal the intervention performed, and participants will be told not to reveal the type of treatment received. The intervention will be given a number code, so that it cannot be identified.

  The statistical consultant will also not know what intervention is assigned to each patient, in this way, the detection bias will be reduced.
- The fact that the presence of a stenosis or not on the uroflowmetry, or even on the RUG-VCUG have no clear criteria may seem subjective and therefore a limitation. However, as this evaluation is carried out by urologists or radiologists' experts specialized in urethral stricture, the bias is reduced.

- The fact that the whole process will not be carried out in HUDJT, and some interventions, such the MukoCell® growth, will be performed by another team in another country, can be a limitation. Nevertheless, the fact that this product is already in process of being accepted by the EMA and is produced in a GMP laboratory, this makes it possible for the pilot clinical trial to be done in our hospital, after having the acceptation by the EMA and the AEMPS afterwards.
- It would be interesting in the future to create a multi-center study in order to increase the sample size to enhance statistical power and reduce recruitment time.
- Another limitation is the costs put into the study as it is expensive. However, it can change many patients' outcomes for the better if results are conclusive. High cost and lack of off-the-shelf availability are the major disadvantages of the technique, but appropriate scientific development and careful commercialization will help circumvent theses aspects.
- An additional limitation to keep in mind, presented in all clinical trials, is the external validity. Even though, we believe that this study could be extrapolated to our population, further multi-centered studies should be carried out in the future to reduce this limitation. Regarding internal validity, all the covariates will be controlled, and taken into account, to reduce it.

Even though the urological team is made up by several specialists, they will have received sufficient training to standardize the procedure of the techniques, thus avoiding the variability between procedures.

Apart from that, due to the randomization process, both groups will be similar and comparable to each other.

# FEASIBILITY

We have considered this study feasible from different perspectives. First of all, the main research team conducting this trial study is a group of prepared urologists, trained in this subject, to whom it will be explained all the steps of this clinical trial.

The main investigator will be prepared to carry out the organization of this clinical trial as well.

As it involves only the HUDJT, it makes it easy to control the different techniques made out for the different professionals, this will also involve the fact that the meetings are going to be much easy to carry out. The hospital itself can provide much of the equipment, and staff.

All computers and database development programs to carry out to test the analysis of these are also in the same hospital.

In cases where any emergency complication should be re-intervened or treated, the hospital is able to assume this cost and responsibility.

A total of 25 patients are presented with an anterior urethral stricture in the Girona Health Region (including the main hospitals and the HUDJT), which means that in a total of 5 years and 6 months, we would be able to achieve the total recruitment of patients. Two more extra years are needed to be able to carry out the data collection of the required sample.

All patients will be given an information sheet and an informed consent before entering the study. As the surgeon and the patient know in which group of the study are going to be located, the type of urethroplasty is given a procedure code as well, and the patient himself is given a number ID. At the same time the patients will be randomly assigned to the procedures, and they will be asked to not inform the doctor doing the follow-ups, who at the same time will not know the procedure the patient underwent.

# IMPACT OF THE STUDY IN THE NATIONAL SYSTEM

We believe that this clinical trial will have an impact on the national health system as the new product used (MukoCell®), may end up replacing in the future the technique currently used (BMG urethroplasty), and become the gold standard procedure for treating patients who present with an anterior urethral stricture.

This is due to the decrease in complications produced in the oral mucosa, and the symptomatic improvement, as in the various functional tests, improving patients' quality of life.

It should be noted that in those large strictures, the oral mucosa is limited in extraction, so the use of this new product will improve the outcome int these patients significantly.

The fact that the time of the lithotomy position during the surgery is reduced, decreases the number of complications that could appear until now.

It should also be noted that in this new technique, total anesthesia may not be necessary, which would allow us to treat a greater number of patients in the future, as well as to improve other techniques related to this treatment.

We also take into account that the introduction of a new product in the national health system would reduce its cost by standardizing its marketing.

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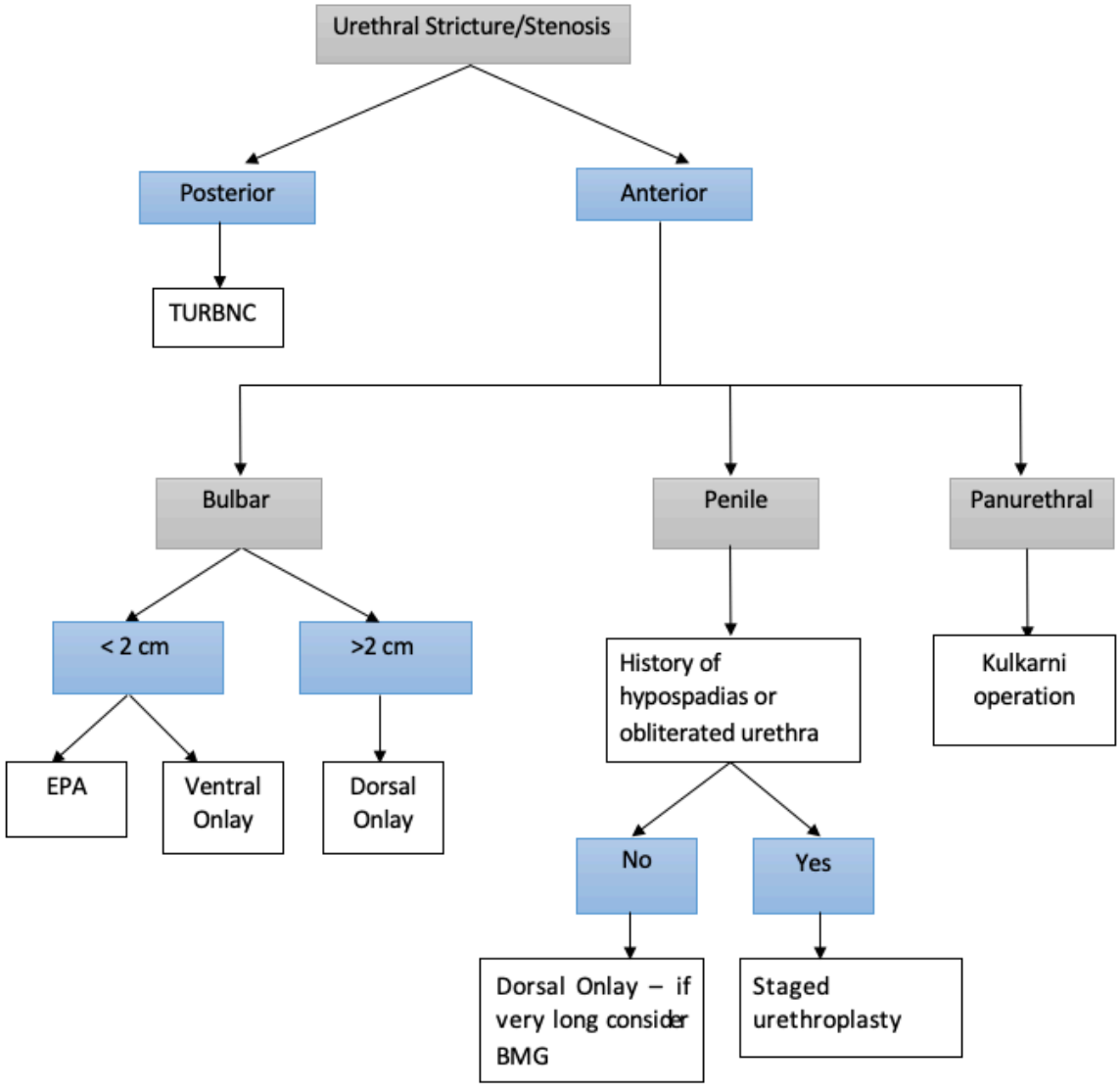
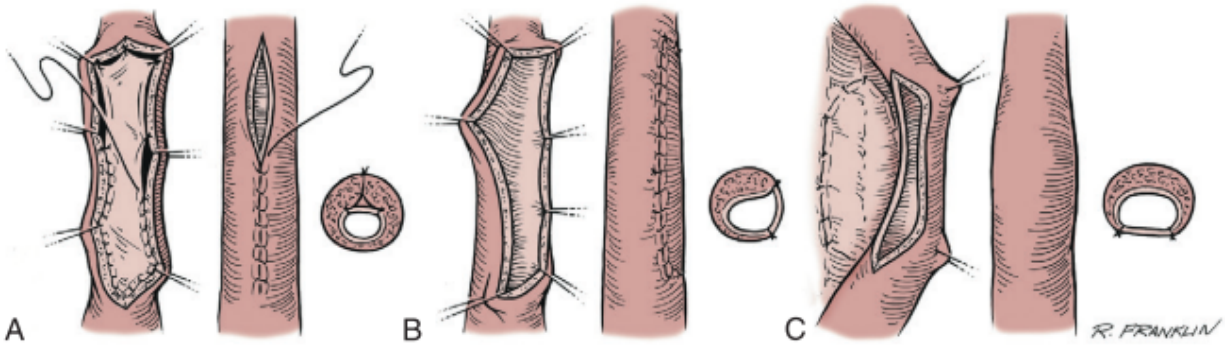
# ANNEXES

## Annex 1. A summary of urethral stricture treatments.



## Annex 2. Urethroplasty step by step

**Where to locate the graft?**

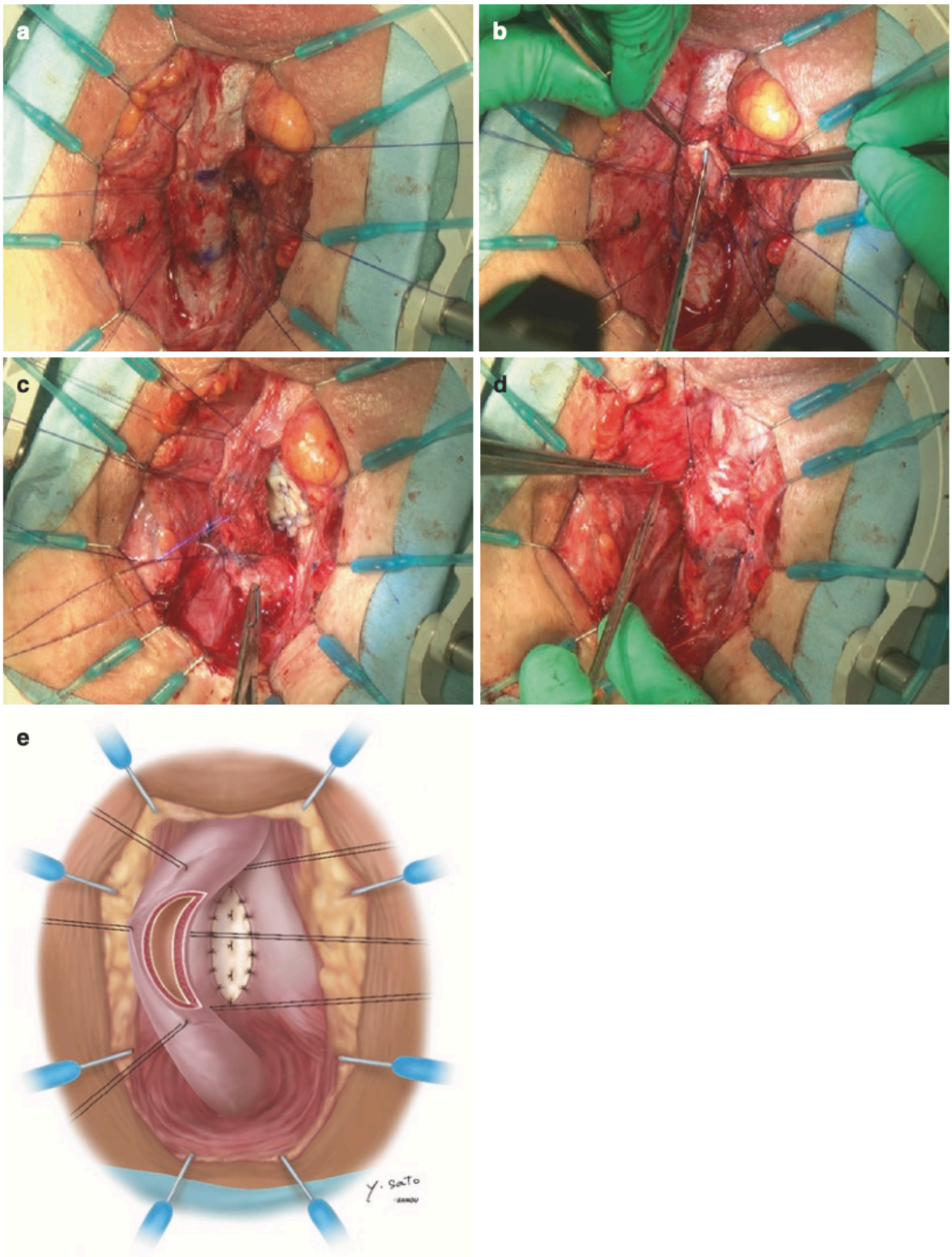



A: Ventral Onlay with spongioplasty

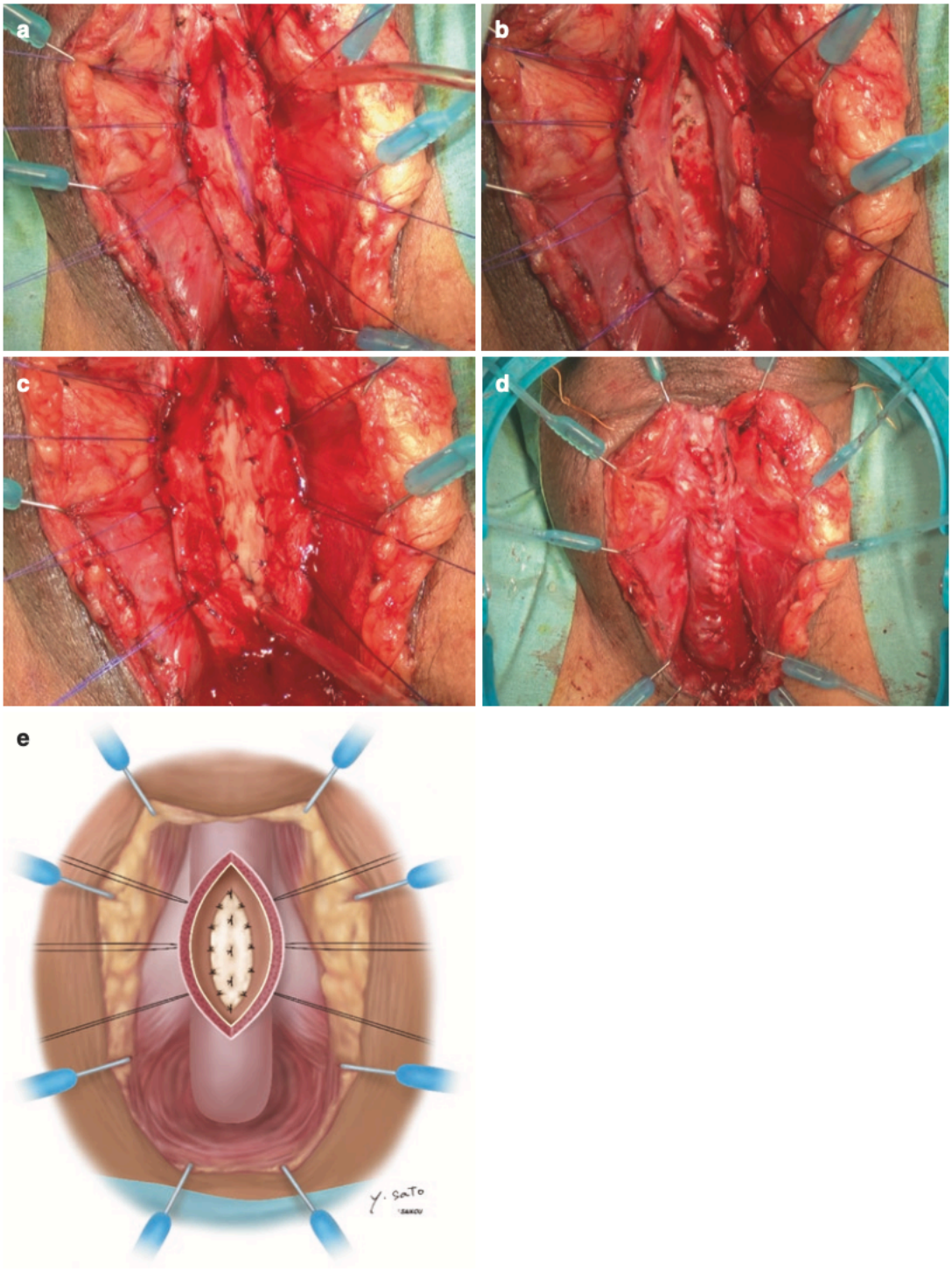
B: Lateral onlay with quilting to ischicavernosus muscle

C: Dorsal onlay with spread fixation of the graft

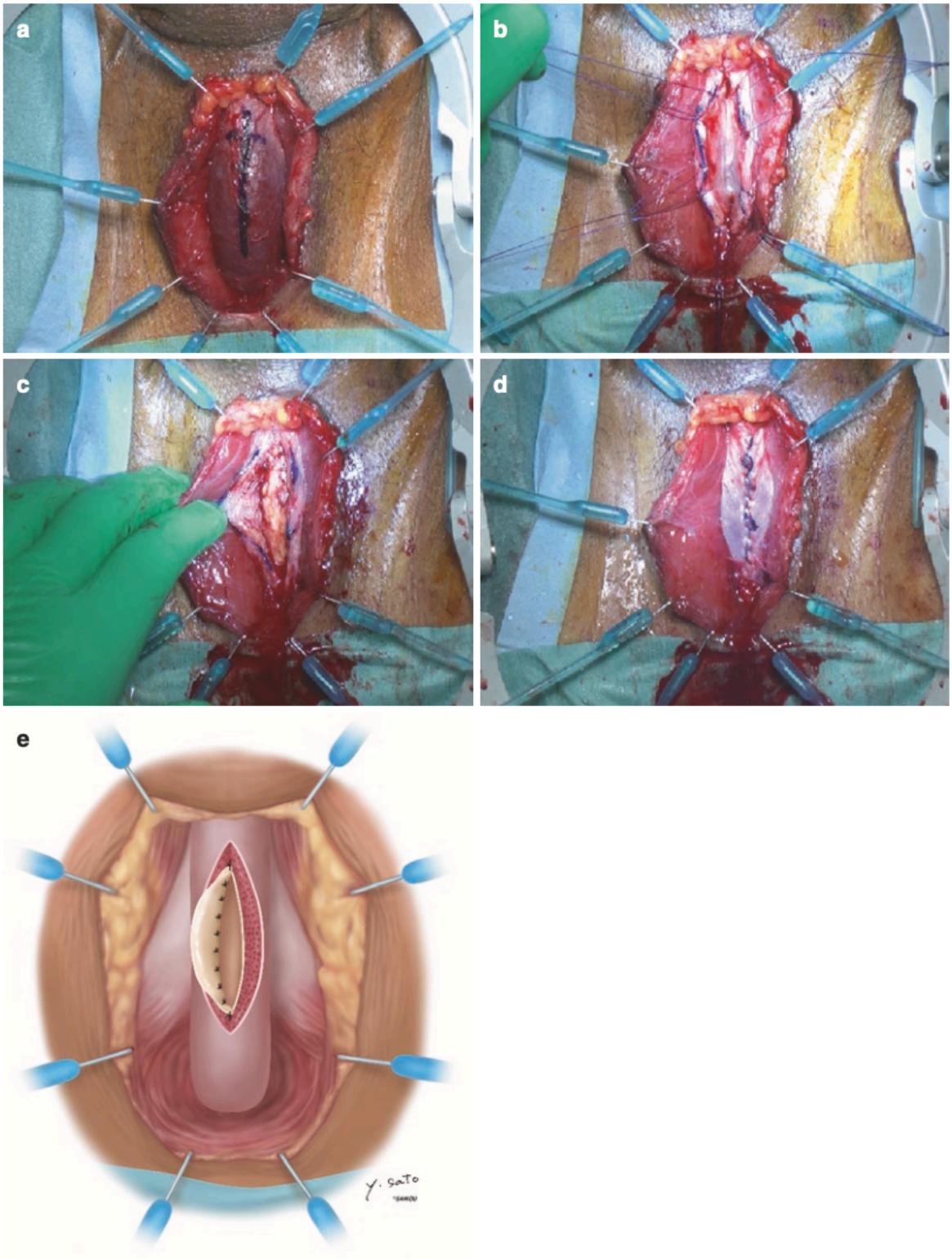
**Step-by-step urethroplasty using BMG**




**Dorsal Onlay:** a) The bulbar urethra is circumferentially mobilized and rotated. b) The dorsal urethral surface is incised along the midline to expose the entire stricture. c) The graft is spread, fixed over the corpora cavernosa. d) The bulbar urethra is rotated back, and the margin of the graft is sutured to the margin of the urethral mucosal plate. e) Schematic image of dorsal onlay.




**Dorsal Inlay:** a) The urethra is left adherent to the corpora cavernosa and is longitudinally opened ventrally expanding to the distal and proximal healthy urethra. B) The stricture urethral plate is longitudinally opened dorsally. C) The graft is sutured to the margins of the urethral plate and fixed to the corpora cavernosa. D) the urethra is retubularized over a urethral catheter. E) Schematic image of dorsal inlay.




**Ventral Onlay:** a) The corpus spongiosum is opened along its ventral surface and b) the urethral lumen is fully exposed, extending the urethrotomy and proximally to the stenosis. c) The graft is sutured to the edge of the urethral mucosa plate. d) The spongiosum tissue is closed over the graft. e) Schematic image of ventral onlay.

## Annex 3. PROM-USS: Patient reported outcome measure for urethral stricture surgery

Gracias por completar este cuestionario. Las siguientes preguntas están diseñadas para medir el efecto que la estrechez de la uretra tiene sobre la vida de los pacientes.

A pesar de que algunas preguntas puedan parecer similares, en realidad no lo son. Rogamos emplee unos minutos de su tiempo para rellenar correctamente el cuestionario señalando la respuesta que mejor describa sus síntomas miccionales **durante el último mes**. Si actualmente es portador de una sonda vesical o catéter suprapúbico, por favor comience directamente en la página 4.

1.- Una vez decide orinar, ¿nota un retraso en el comienzo de la micción?

- Nunca ☐
- Ocasionalmente ☐
- A veces ☐
- La mayoría de las veces ☐
- Siempre ☐

2.- Describiría la fuerza de su chorro de orina como...

- Normal ☐
- Disminuida ocasionalmente ☐
- Disminuida a veces ☐
- Disminuida la mayoría de las veces ☐
- Disminuida siempre ☐

3.- ¿Necesita hacer fuerza / presión abdominal para seguir orinando?

- Nunca ☐
- Ocasionalmente ☐
- A veces ☐
- La mayoría de las veces ☐
- Siempre ☐

4.- Mientras orina, ¿tiene que parar y empezar de nuevo más de una vez?

- Nunca ☐
- Ocasionalmente ☐
- A veces ☐
- La mayoría de las veces ☐
- Siempre ☐

5.- ¿Con qué frecuencia, después de haber terminado de orinar, tiene la sensación de no haber vaciado completamente la vejiga?

- Nunca ☐
- Ocasionalmente ☐
- A veces ☐
- La mayoría de las veces ☐
- Siempre ☐

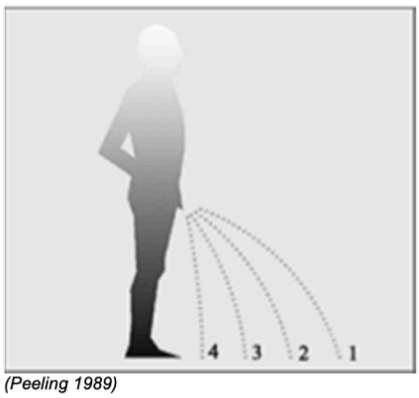
6.- ¿Con qué frecuencia ha notado haber mojado/manchado los calzoncillos unos minutos después de haber orinado y haberse subido los pantalones?

- Nunca ☐
- Ocasionalmente ☐
- A veces ☐
- La mayoría de las veces ☐
- Siempre ☐

7.- En general, ¿cuánto diría que afectan a su vida sus síntomas urinarios?

| | |
|---|---|
| Nada | ☐ |
| Un poco | ☐ |
| Bastante | ☐ |
| Mucho | ☐ |

8.- Marque con un círculo el número que correspondería a la fuerza de su chorro miccional en el último mes.



*(Peeling 1989)*

9.- ¿Está usted satisfecho con el resultado de la intervención?

| | |
|---|---|
| Sí, muy satisfecho | ☐ |
| Sí, satisfecho | ☐ |
| No, insatisfecho | ☐ |
| No, muy insatisfecho | ☐ |

10.- En caso de estar insatisfecho o muy insatisfecho es porque:

| | |
|---|---|
| La situación miccional no ha mejorado. | ☐ |
| La situación miccional ha mejorado pero ha habido otros problemas. | ☐ |
| La situación miccional no ha mejorado y además ha habido otros problemas. | ☐ |

Marque con una cruz la opción de cada grupo que mejor describa su estado de salud a día de hoy:

**Movilidad**:

| | |
|---|---|
| No tengo problemas al andar | ☐ |
| Tengo algunos problemas al andar | ☐ |
| No puedo andar y estoy en cama | ☐ |

**Autocuidado**:

| | |
|---|---|
| No tengo problemas con mi autocuidados | ☐ |
| Tengo algunos problemas con mi higiene personal y al vestirme | ☐ |
| No puedo lavarme o vestirme por mí mismo | ☐ |

**Actividades cotidianas (empleo, trabajo en casa, estudio, deporte,...):**

| | |
|---|---|
| No tengo problemas al realizar mi actividades cotidianas | ☐ |
| Tengo algunos problemas al realizar mis actividades cotidianas | ☐ |
| No puedo realizar mis actividades cotidianas | ☐ |

**Dolor/molestias:**

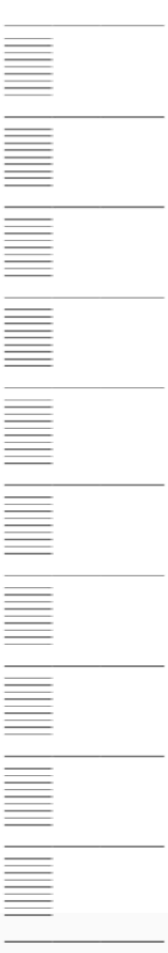
| | |
|---|---|
| No tengo dolor ni molestias | ☐ |
| Tengo dolor o molestias moderados | ☐ |
| Tengo mucho dolor o molestias | ☐ |

**Ansiedad/depresión:**

| | |
|---|---|
| No estoy ansioso o deprimido | ☐ |
| Estoy moderadamente ansioso o deprimido | ☐ |
| Estoy muy ansioso o deprimido | ☐ |

Para ayudarnos a saber cómo de bueno o malo es su estado de salud hemos dibujado una escala (como un termómetro) en la que el 100 correspondería al mejor estado de salud que pueda imaginar y el 0 al peor.

Nos gustaría que nos indicara como de bien o mal piensa que está su estado de salud a día de hoy.




100 Mejor estado de salud imaginable

0 Peor estado de salud imaginable

## Annex 4. IPPS: International Prostate Symptom Score

**IPSS (Puntuación internacional de los síntomas prostáticos)**

| | Ninguna | Menos de 1 vez de cada 5 | Menos de la mitad de veces | Aproximada-mente la mitad de veces | Más de la mitad de veces | Casi siempre |
|---|---|---|---|---|---|---|
| 1.- Durante más o menos los últimos 30 días, ¿cuántas veces ha tenido la sensación de no vaciar completamente la vejiga al terminar de orinar? | O. ☐ | I. ☐ | 2. ☐ | 3. ☐ | 4. ☐ | 5. ☐ |
| 2.- Durante más o menos los últimos 30 días, ¿cuántas veces ha tenido que volver a orinar en las dos horas siguientes después de haber orinado? | O. ☐ | I. ☐ | 2. ☐ | 3. ☐ | 4. ☐ | 5. ☐ |
| 3.- Durante más o menos los últimos 30 días, ¿cuántas veces ha notado que, al orinar, paraba y comenzaba de nuevo varias veces? | O. ☐ | I. ☐ | 2. ☐ | 3. ☐ | 4. ☐ | 5. ☐ |
| 4.- Durante más o menos los últimos 30 días, ¿cuántas veces ha tenido dificultad para aguantarse las ganas de orinar? | O. ☐ | I. ☐ | 2. ☐ | 3. ☐ | 4. ☐ | 5. ☐ |
| 5.- Durante más o menos los últimos 30 días, ¿cuántas veces ha observado que el chorro de orina es poco fuerte? | O. ☐ | I. ☐ | 2. ☐ | 3. ☐ | 4. ☐ | 5. ☐ |
| 6.- Durante más o menos los últimos 30 días, ¿cuántas veces ha tenido que *apretar o* hacer fuerza para comenzar a orinar? | O. ☐ | I. ☐ | 2. ☐ | 3. ☐ | 4.D | 5.D |
| | Ninguna | Ivez | 2 veces | 3 veces | 4 veces | 5 o más veces |
| 7.- Durante más o menos los últimos 30 días, ¿cuántas veces suele tener que levantarse para orinar desde que se va a la cama por la noche hasta que se levanta por la mañana? | O. ☐ | I. ☐ | 2. ☐ | 3. ☐ | 4. ☐ | 5. ☐ |

PUNTUACIÓN IPSS TOTAL:

| | Encantado | Muy satisfecho | Más bien satisfecho | Tan satisfecho como insatisfecho | Más bien insatisfecho | Muy insatisfecho | Fatal |
|---|---|---|---|---|---|---|---|
| 8.- ¿Cómo se sentiría si tuviera que pasar el resto de la vida con los síntomas prostáticos tal y como los siente ahora? | O. ☐ | I. ☐ | 2. ☐ | 3. ☐ | 4. ☐ | 5. ☐ | 6. ☐ |

## Annex 5. SHIM (IIEF-5): Sexual Health inventory for men/International Index Erectile Function

**The IIEF-5 Questionnaire (SHIM)**

**Please encircle the response that best describes you for the following five questions:**

| **Over the past 6 months:** | | | | | |
|---|---|---|---|---|---|
| 1. How do you rate your confidence that you could get and keep an erection? | Very low<br>1 | Low<br>2 | Moderate<br>3 | High<br>4 | Very high<br>5 |
| 2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration? | Almost never or never<br>1 | A few times (much less than half the time)<br>2 | Sometimes (about half the time)<br>3 | Most times (much more than half the time)<br>4 | Almost always or always<br>5 |
| 3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated your partner? | Almost never of never<br>1 | A few times (much less than half the time)<br>2 | Sometimes (about half the time)<br>3 | Most times (much more than half the time)<br>4 | Almost always or always<br>5 |
| 4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse? | Extremely difficult<br>1 | Very difficult<br>2 | Difficult<br>3 | Slightly difficult<br>4 | Not difficult<br>5 |
| 5. When you attempted sexual intercourse, how often was it satisfactory for you? | Almost never or never<br>1 | A few times (much less than half the time)<br>2 | Sometimes (about half the time)<br>3 | Most times (much more than half the time)<br>4 | Almost always or always<br>5 |

**Total Score:** _____

1-7: Severe ED 8-11: Moderate ED 12-16: Mild-moderate ED 17-21: Mild ED 22-25: No ED

## Annex 6. Clavien-Dindo classification

**Table 1: Clavien-Dindo classification.**

| Grades | Definitions of grades | Modes of therapy |
|---|---|---|
| **Grade I** | Any deviation from the normal postoperative course. | No pharmacological or surgical treatment, endoscopic or radiological interventions were required. Acceptable therapeutic regimens are drugs such as anti-emetics, antipyretics, analgesics, diuretics, and electrolytes and physiotherapy. Wound infections or small abscess requiring incision at bedside is within this category. |
| **Grade II** | Normal course altered | Pharmacological management other than in Grade 1. Blood transfusions and total parenteral nutrition are also included. |
| **Grade III** | Complications that require intervention of various degrees | Sub-classified into:<br>Grade IIIa – complications that require an intervention performed under local anaesthesia.<br>Grade IIIb – interventions that require general or epidural anaesthesia. |
| **Grade IV** | Complications threatening life of patients (including CNS complications), requiring ITU support | Further sub-classified into:<br>Grade IV a – single organ dysfunction (including dialysis).<br>Grade IV b – multi-organ dysfunction. |
| **Grade V** | Death of a patient | |

## Annex 7. Body Mass Index (BMI)

| **Weight Status Category** | **BMI Range** (kg/m²) |
|---|---|
| Underweight | Below 18.5 |
| Healthy weight | 18.5 to 24.9 |
| Overweight | 25 to 29.9 |
| Obese | 30 or greater |

## Annex 8. ASA physical status classification

| **ASA grade** |
|---|
| I Normal healthy patient |
| II Patient with mild systemic disease |
| III Patient with severe systemic disease |
| IV Patient with severe systemic disease that is constant threat to life |
| V Moribund patient who is not expected to survive without the operation |
| VI Declared brain-dead patient whose organs are being removed for donor purposes |

## Annex 9. Information sheet for patients

**EXPLANATORY DOCUMENT FOR THE PARTICIPANT (Catalan)**

| |
|---|
| Nom de l'estudi: Estudiar la millora de l'ús del MukoCell® en uretroplàsties, en comparativa amb injert de mucosa bucal, en estenosis de uretra bulbar, superiors a 2,5 cm. |
| Centre assistencial: |
| Investigador/a principal: |

Benvolgut/da,

Ens adrecem a vostè per agrair-li la seva participació en el següent projecte de recerca:

**Buccal mucosa graft versus MukoCell® technique urethroplasty**

**Introducció i objectiu de l'estudi**

Ens dirigim a vostè per informar-li sobre el nostre estudi de investigació que es durà a terme en el servei de Urologia de l'Hospital Dr. Josep Trueta de Girona, al que se li convida a participar.

Aquest projecte té com a objectiu reduir els resultats post-intervenció en el context de una estenosis d'uretra bulbar, intervinguda a través de una uretroplàstia amb l'ús d'injert de mucosa bucal.

D'aquest manera, podríem millorar els aspectes del tractament de les uretroplàsties anteriors, i en un possible futur intentar reduir les complicacions que se'n esdevenen, millorant els resultats, i per tant, els símptomes i la qualitat del vida dels molts pacients que veuen afectada la seva vida per aquesta malaltia.

**Descripció de l'estudi**

Primerament, informar que aquest projecte ha estat aprovat pel Comitè d'Ètica Investigació Clínica (CEIC) i la AEMPS (Asociación Española de Medicamentos y productos sanitarios).

En aquest estudi hi participaran aproximadament uns 132 participants. Llavors, de manera aleatoritzada, en l'hospital d'ingrés (Hospital Universitari Doctor Josep Trueta de Girona), formarem dos grups de les quals es modificarà el seu tractament sobre la estenosis de uretra.

- Al primer grup, se li durà a terme una biòpsia de la mucosa bucal, per a poder utilitzar a posteriori el mètode MukoCell®, per tractar la uretroplàstia.
- A l'altre grup es durà a terme una uretroplàstia convencional, utilitzant un injert de mucosa bucal, extreta el mateix dia de la intervenció.

Cal tenir present, que en cap dels dos grups la recuperació i millora del pacient es veurà repercutida o afectada.

Un cop superat el procediment quirúrgic, tots els pacients participants de l'estudi tindran quatre visites de seguiment on se'ls hi realitzaran unes exploracions invasives i no-invasives, juntament amb varies escales d'aproximació clínica i diagnòstica que ens ajudarà a veure l'efectivitat o no de les tècnica aplicada.

**Participants en el projecte**

Degut a la presència de la estenosis de uretra, se'l convida a participar en aquest projecte:

- De totes les maneres, dependent de l'evolució, les dades només quedaran incloses a l'estudi si presenta els criteris de inclusió necessaris en tot moment.

La participació en l'estudi inclourà quatre visites de seguiment d'aproximadament 30 minuts-1 hora de durada, una post-intervenció, al 8è dia, als 6 i 12 mesos, i als 2 anys, per avaluar diferents aspectes de l'estenosi de uretra.

**Riscs de l'estudi**

En la part en que s'utilitzen intervencions no-invasives ni farmacològiques, no es preveu cap ric físic pels participants.

Pel que fa les intervencions invasives, com la pròpia tècnica d'uretroplàstia, juntament amb el cultiu de la mucosa bucal, els riscos són els mateixos per ambdues tècniques.

El risc que hi pot haver al tractar mostres biològiques durant la biòpsia de mucosa bucal s'evitarà amb la Llei d'Investigació biomèdica. Igualment el potencial risc estaria en relació amb la confidencialitat de les seves dades clíniques, que s'evitarà sent tractades d'acord amb la Llei de Protecció de Dades.

**Possibles beneficis de l'estudi**

El benefici de tots els participants seria el de l'avenç de la medicina en benefici de la societat i el coneixement de que ha col·laborat en aquest procés. Si vostè ho desitgés, se li facilitaria un resum dels resultat de l'estudi.

L'investigador no obtindrà remuneració econòmica per realitzar l'assaig clínic.

**Confidencialitat**

Finalment, al acceptar la seva participació, vostè permetria al seu investigador a registrar algunes dades de la seva història clínica. Tota informació utilitzada en l'estudi serà codificada mantenint la dissociació de les seves dades, l'anonimat i tractades segons la Llei de Protecció de Dades 3/2018. No s'utilitzaran noms o dades on es puguin identificar participants, tots els resultats de la resta d'exàmens complementaris i les dades de la historia clínica seran tractades amb total confidencialitat.

Tant l'hospital com l'investigador són responsables respectivament del tractament de les seves dades i es comprometen a complir amb la normativa de protecció de dades en vigor.

Els comitès d'Ètica de la investigació, els representants de l'autoritat sanitària en matèria d'inspecció i el personal autoritzat per l'investigador, únicament podran accedir per comprovar les dades personals, els procediments de l'estudi clínic i el compliment de les normes de bona pràctica clínica, mantenint la confidencialitat en tot moment.

D'acord al que s'estableix en la legislació esmentada, vostè pot exercir als drets d'accés, rectificació, oposició i cancel·lació de dades en qualsevol moment. Vostè també pot limitar el tractament de dades que siguin incorrectes, sol·licitar una copia o que es traslladin a un tercer (portabilitat) les dades que vostè ha facilitat per a l'estudi. Per exercitar els seus drets, pot dirigir-se al metge responsable de l'estudi, o si s'escau a l'Agència Espanyola de Protecció de Dades (AEPD).

L'investigador està obligat a conservar les dades recollides per a l'estudi a almenys durant 5 anys després de la seva finalització. Posteriorment, la seva informació personal només es conservaria al centre per a la cura de la seva salut i per l'investigador per a altres fins d'investigació científica si vostè hagués atorgat el seu consentiment per a això, i si així ho permet la llei i els requisits ètics aplicables.

**Difusió dels resultats**

Un cop s'hagi completat tot l'estudi es preveu una anàlisi de les dades i una extracció de resultats. Les conclusions del projecte seran sotmesos a publicacions científiques, independentment d'un resultat favorable o desfavorable.

Com comentant anteriorment, sense cap dada que pugui portar a la identificació del subjecte.

**Participació i compensació econòmica**

Cal tenir present que la participació en aquest estudi és voluntària. Per tant, si vostè decideix participar no rebrà cap tipus de compensació econòmica. En el cas contrari, tampoc implicarà un canvi a la seva atenció mèdica per part dels diferents especialistes.

Abans de participar, caldrà que firmi un consentiment informat on confirma que ha llegit el document explicatiu i està d'acord amb el projecte. En el cas que el pacient vulgui deixar de participar en l'estudi, ho podrà fer mitjançant la revocació del consentiment informat, un document que podrà demanar a qualsevol membre de l'estudi. Igual que participar en l'estudi clínic, sortir de l'estudi és voluntari, sense necessitats de donar explicacions i amb la seguretat que en cap cas comprometrà la seva atenció mèdica ni el curs del seu tractament.

Respecte les seves dades, vostè pot retirar en qualsevol moment el consentiment sobre el tractament de les seves dades. Així mateix, té dret a dirigir-se a l'AEPD si no quedés satisfet.

**Contacte**

En cas de qualsevol dubte o pregunta durant la realització d'aquest estudi, podrà posar-se en contacte amb el responsable i coordinador de l'estudi:

## Annex 10. Consent form to enter the trial

| | | |
|---|---|---|
| Hospital Universitari de Girona Doctor Josep Trueta<br><br>Av. França s/n 17007 Girona | CONSENTIMENT INFORMAT | Buccal mucosa graft versus MukoCell® technique urethroplasty |

**CONSENTIMENT INFORMAT**

Jo (Nom i cognoms) _____ amb DNI _____.

- He llegit la fulla informativa que se m'ha entregat sobre l'estudi.
- He pogut fer preguntes sobre l'estudi.
- He rebut suficient informació sobre l'estudi.
- He parlat amb: (nom de l'investigador): _____
- Comprenc que la meva participació és voluntària
- Comprenc que els resultats obtinguts seran guardats per mantenir la confidencialitat de les meves dades d'acord amb la Llei de Biomèdica de 2018 (Ley 03/2018 de Investigación Biomédica).
- Comprenc que puc revocar el meu consentiment en qualsevol moment, sense haver de donar explicacions i sense que alteri la meva assistència sanitària.

Accedeix a que els investigadors principals del projecte puguin contactar amb vostè en un futur si ho consideren oportú.

Dono lliurement la meva conformitat per participar en l'estudi i dono el meu consentiment per l'accés I utilització de les meves dades en les condicions detallades en la fulla de informació.

Si ☐ No ☐

Firma del pacient:

Data: ___/___/___

Firma de l'investigador:

Data: ___/___/___

Firma del representant legal,

familiar o persona vinculada al fet:

Data: ___/___/___

Firma de l'investigador:

Data: ___/___/___

**CONSENTIMENT INFROMAT URETROPLÀSTIA BULBOMEMBRANOSA**

| | | |
|---|---|---|
| Hospital Universitari de Girona Doctor Josep Trueta<br><br>Av. França s/n 17007 Girona | CONSENTIMENT INFORMAT | Buccal mucosa graft versus MukoCell® technique urethroplasty |

Cognoms

Nom

Data de naixement Sexe

NHC DNI

CIP

Episodi Origen

**Nom del procediment**

Uretroplàstia bulbomembranosa

**Descripció del procediment**

Mitjançant aquest procediment es pretén la millora en la qualitat miccional alterada per la presència d'una estenor completa o parcial de la uretra, així com la supressió de la sonda vesical permanent si en fos portador d'aquesta (tant si és uretral com de talla suprapúbica). A més, comprenc que en el millor dels casos, per la pròpia naturalesa de la malaltia, pot ser necessari realitzar dilatacions uretrals periòdiques (i en alguns casos altres intervencions). El metge m'ha explicat que el procediment requereix l'administració d'anestèsia i, que és possible què, durant o després de la intervenció, sigui necessària la utilització de sang i/o hemoderivats, d'aquests riscos m'informaran els serveis d'anestèsia i hematologia. Mitjançant aquesta tècnica es tracta l'estenosi d'uretra. L'estenosi és una cicatriu interior de la uretra que disminueix el calibre d'aquesta i pot ser deguda a diverses causes: congènita (habitualment detectada en la infància), infeccions, traumatismes o com a seqüela de la cirurgia transuretral prèvia o sondatges. La tècnica consisteix en obertura de la uretra a nivell del penis o perineu, amb escissió del segment que presenta l'estenosi. Dependent de la localització i longitud de l'estenosi es pot realitzar la reconstrucció en un sol temps o bé, pot ser necessari deixar la uretra oberta per facilitar la seva regeneració procedint a la reconstrucció definitiva en un segon temps. En aquesta reconstrucció cal de vegades utilitzar altres teixits, com la mucosa de la boca o la pròpia pell del penis.

**Riscos Específics més freqüents**

Comprenc què, tot i l'adequada elecció de la tècnica i de la correcta realització, es poden presentar efectes indesitjables, tant els comuns derivats de tota intervenció i que poden afectar tots els òrgans i sistemes, com altres específics del procediment com per exemple, no aconseguir millora en la qualitat miccional o no poder retirar la sonda vesical permanent, si en fos porta d'aquesta; el desenvolupament d'una estenosi uretral que requerirà tractaments posteriors entre els que pot estar indicat el procedir a la realització d'un meat perineal permanent; incontinència urinària que pot ser total i permanent, parcial i permanent, total i temporal o parcial i temporal; perforació d'uretra durant l'acte quirúrgic, que provoqui extravasació del líquid d'irrigació cap a les estructures periuretrals, amb la possibilitat de formació de un abscés (de succeir aquesta complicació, caldrà realitzar urgent i necessària d'una altra intervenció diferent); hemorràgia incoercible, tant durant l'acte quirúrgic com en el posteriori les conseqüències són molt diverses, depenent del tipus de tractament que es necessiti, i oscil·len des d'una gravetat mínima fins a la possibilitat certa de mort, com a conseqüència directa del sagnat o per efectes secundaris dels tractaments emprats; fístules uretrals, el tractament pot ser complex, amb sonda i/o intervencions successives; perforació del recte el tractament obliga a realitzar una intervenció diferent consistent en una laparotomia (obertura de l'abdomen) de conseqüències imprevisibles on s'inclou, encara que remotament, la possibilitat de mort (habitualment cal associar a la laparotomia la realització d'una colostomia (anoartificial) temporal o definitiva; impotència total o parcial; tromboembolismes venosos profunds o pulmonars la gravetat depèn de la intensitat del procés; hemorràgies digestives que són infreqüents, però presents encara que es prenguin mesures profilàctiques i la gravetat depèn de la seva intensitat.

El metge m'ha explicat que aquestes complicacions habitualment es resolen amb tractament mèdic (medicaments, sèrums...), però poden arribar a requerir una re intervenció, generalment d'urgència, incloent-hi risc de mortalitat. El metge m'ha explicat que per a la realització d'aquesta tècnica pot ser necessària una preparació, de vegades amb peculiaritats com _____ encara que pot ser possible la seva realització sens una preparació completa.

**Observacions i Contraindicacions**

També m'han explicat la necessitat d'advertir de les meves possibles al·lèrgies medicamentoses, alteracions de la coagulació, malalties cardiopulmonars, existència de pròtesis, marcapassos, medicacions actuals o qualsevol altra circumstància. En cas de (diabetis, obesitat, hipertensió,

anèmia, edat avançada) pot augmentar la freqüència o la gravetat de riscos o complicacions com

_____

**Riscos personals i professionals**

A més dels riscos ja descrits, per les meves circumstàncies especials, mèdiques o d'altre tipus, es poen esperar els següents riscos: _____

**Procediments alternatius**

El metge m'ha explicat que altres alternatives són la uretrostomia endoscòpica, la pròtesi i les dilatacions periòdiques, però que en el meu cas la millor alternativa terapèutica és la uretroplàstia.

**Autorització**

Declaro que he estat informat pel metge dels aspectes més important de la intervenció quirúrgica que se'm va a realitzar, de la seva normal evolució, de les possibles complicacions i riscos de la mateixa, de les seves contraindicacions, de les conseqüències que es derivarien en el cas que no em sotmetés a l'esmentada intervenció i de les alternatives a aquesta tècnica quirúrgica. Estic satisfet/a de la informació rebuda. He pogut formular totes les preguntes que he cregut convenients i m'han estat aclarits tots els dubtes plantejats. Declaro, a més, no haver ocultat informació essencial sobre el meu cas, els meus hàbits, o regim de vida, que poguessin ser rellevants als metges que m'atenen. Sé, per altra banda que m'intervindrà el facultatiu que, fins de les circumstàncies de l'equip mèdic en el dia de la intervenció, sigui el més adequat per al meu cas. Per tot això, DONO EL MEU CONSENTIMENT PER A SER OPERAT, així com per què, durant la intervenció, el cirurgià prengui les mostres biològiques que consideri necessàries per a l'estudi del meu procés, o les imatges necessàries per l'aquedada documentació el cas. En el cas que, durant la intervenció, el cirurgià trobi aspectes de la meva malaltia que li exigeixin o li aconsellen modificar el procediment inicialment projectat, podrà fer-ho de la manera que millor convingui al meu estat de salut, advertint a la meva família o, si no n'hi ha, prenent la decisió per ell mateix. També entenc que, tot i els nombroses i acurades mesures d'higiene de l'equip assistencial que m'atén, l'acte quirúrgic i l'estada a l'hospital són un factor de les anomenades infeccions hospitalàries, que són excepcionals, però possibles. Conec, d'una altra banda, el meu dret a revocar aquesta autorització en qualsevol moment. Aquest consentiment es formula d'acord amb el que s'estableix en la Llei 21/2000 de 29 de desembre publicada al DOGC núm. 3303 de l'11 de gener del 2001.

**Servei sol·licitant** **Professional que informa** **Número d'identificació**

**Signatura i DNI el/la pacient o responsable** **Data** **Signatura del professional**

☐ Accepta

☐ No accepta

**Revocació consentiment informat**

Jo, En/Na _____ revoco el consentiment prestat en data _____ i declaro per tant, que després de la informació rebuda, no autoritzo a sotmetre'm al procediment de uretroplàstia bulbomembranosa.