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Reviews

Bioengineering solutions for ureteric disorders: clinical need, challenges and opportunities

Konstantinos Kapetanos[1], Alexander Light[2], Niyukta Thakare[2], Krishnaa Mahbubani[3,4], Kasra Saeb-Parsy[2] and Kourosh Saeb-Parsy[5]

[1]School of Clinical Medicine and [4]Department of Haematology, University of Cambridge, [2]Department of Urology, Cambridge University Hospitals NHS Foundation Trust, [3]Cambridge Biorepository for Translational Medicine (CBTM), NIHR Cambridge Biomedical Research Centre, and [5]Department of Surgery, University of Cambridge and Cambridge NIHR Biomedical Research Centre, Cambridge, UK

Objectives

To summarise the causes of ureteric damage and the current standard of care, discussing the risks and benefits of available therapeutic options. We then focus on the current and future solutions that can be provided by ureteric bioengineering and provide a description of the ideal characteristics of a bioengineered product.

Methods

We performed a literature search in February 2021 in: Google Scholar, Medline, and Web of Science. Three searches were conducted, investigating: (a) the epidemiology of ureteric pathology, (b) the current standard of care, and (c) the state of the art in ureteric bioengineering.

Results

The most-common causes of ureteric damage are iatrogenic injury and external trauma. Current approaches to treatment include stent placement or surgical reconstruction. Reconstruction can be done using either urological tissue or segments of the gastrointestinal tract. Limitations include scarring, strictures, and infections. Several bioengineered alternatives have been explored in animal studies, with variations in the choice of scaffold material, cellular seeding populations, and pre-implantation processing. Natural grafts and hybrid material appear to be associated with superior outcomes. Furthermore, seeding of the scaffold material with stem cells or differentiated urothelial cells allows for better function compared to acellular scaffolds. Some studies have attempted to pre-implant the graft in the omentum prior to reconstruction, but this has yet to prove any definitive benefits.

Conclusion

There is an unmet clinical need for safer and more effective treatment for ureteric injuries. Urological bioengineering is a promising solution in preclinical studies. However, substantial scientific, logistic, and economic challenges must be addressed to harness its transformative potential in improving outcomes.

Keywords

Ureteric injury, ureteric reconstruction, tissue engineering, bioengineered solution, #UroTrauma, #Urology

Introduction

Ureteric reconstruction refers to the surgical intervention utilised to correct significant damage to the ureteric tissue resulting from injury or disease. Albeit rare, damage to the ureter can be severe, with potentially devastating complications, including loss of kidney function [1,2]. Rapid and effective management of ureteric damage is critically important for long-term outcomes. There are several accepted surgical approaches that aim to restore structural and functional integrity and continuity of the ureters. Treatments include the introduction of a ureteric stent, and the use of native urological tissue (in the form of ureter or bladder) or intestinal tissue for surgical repair. Although generally successful, most current treatments are associated with potentially serious complications, which continue to drive the pursuit of novel solutions. The field of urological tissue bioengineering offers the tantalising prospect of superior

treatment alternatives. In this review, we will discuss the incidence and aetiology of ureteric disorders and explore the current clinical therapeutic approaches and their outcomes. We will then provide an overview of emerging bioengineering solutions and future directions.

The Clinical Need

The structural and functional integrity of the ureters is commonly compromised as a result of an injury. This includes iatrogenic causes, but it can also be due to the passage of stones or inflicted by traumatic injuries such as a gunshot wound or a high-speed road traffic accident [2,3] (Fig. 1). Subsequently, the injured ureter can develop strictures, perforation, or functional compromise [4]. Although ureteric injuries are relatively rare, they can have severe implications including loss of renal function, if left untreated [5–7].

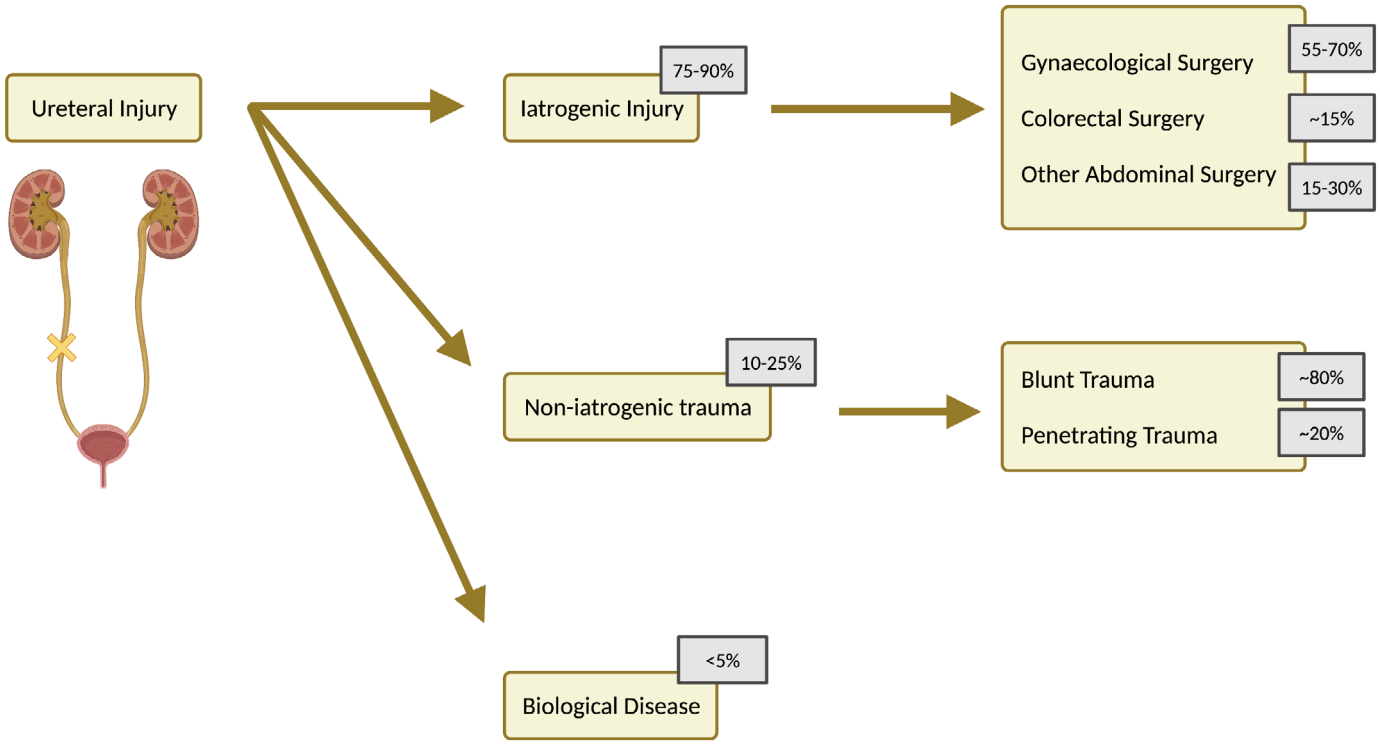
Iatrogenic Injury

Procedures on the gastrointestinal tract or female reproductive system have a high risk of inadvertent damage to the ureters [9]. Importantly, unlike other forms of ureteric injury, iatrogenic cases often have a delayed diagnosis, commonly leading to the development of a more severe phenotype [5,10]. Accordingly, iatrogenic injuries represent the most common cause of ureteric damage that requires reconstruction [11]. The reported incidence of iatrogenic ureteric injury ranges from 0.1% to 3%, depending on the procedure and population investigated [2,12]. Gynaecological procedures, such as hysterectomies, are responsible for the majority of iatrogenic injuries to the ureter, the reported incidence being 0.1–3% globally [5,12,13]. This rate has remained relatively constant over the last three decades and has not significantly changed with the introduction of laparoscopic techniques [14,15]. Consequently, the clinical need in countries such as the USA, in which there are an average of 600 000 hysterectomies in a year, will be much greater than in countries such as the UK, which records a tenth as many [16,17]. Similarly, iatrogenic ureteric injuries are commonly associated with colorectal and urological surgeries, as well as surgeries on the abdominal and pelvic vasculature [2,18].

External Trauma

Genitourinary trauma is observed in ~10% of all trauma cases globally [19], of which ureteric involvement represents 1–3% [7,20,21]. Traumatic ureteric injury is thus rare, as the anatomical position of the ureters, enclosed by bony structures (pelvis and vertebrae) and soft tissues (peritoneum and psoas muscle), combined with their small diameter and high flexibility, offers effective protection from external

Fig. 1 Epidemiology of ureteric injury. Iatrogenic injury comprises the primary causes of ureteric damage, being implicated in 75–90% of cases. Of these, most injuries are inflicted during major gynaecological surgery.



injuries [9]. The causes of traumatic ureteric injuries can be blunt or penetrative, and the precise nature of the damage is causally linked with the nature of the injury [22]. Penetrating injuries usually comprise the majority of cases worldwide [7], particularly in the USA, where there is a higher incidence of gunshot-induced injuries [21]. Patients that experience traumatic injury to the ureter are generally younger, mostly male, and the portion of the ureter that is affected is usually the abdominal segment [7]. This is in contrast to iatrogenic injuries that generally affect older patients and usually involve the distal ureter [23].

Intrinsic Pathology

Retroperitoneal fibrosis is a relatively rare inflammatory condition that affects the ureters in 80–100% of cases [28]. Although surgical reconstruction is one of the available treatments for ureteric involvement in retroperitoneal fibrosis, the incidence of the disease is very low (0.1/100 000 person years) [29]. Although rare, ureteric cancer can compromise ureteric integrity [24]. The reported incidence of upper-tract urothelial carcinoma ranges from 0.6 to 2/100 000 person-years, of which a fifth of cases involve the ureter [25,26]. Risk factors include advancing age, smoking and history of urothelial carcinoma involving the bladder, and survival outcomes are generally poorer with cancer progression [27]. Lastly, ureteric obstruction due to urolithiasis managed endoscopically has a significant risk of development of strictures, which may require surgical reconstruction.

Overall, the incidence of ureteric pathology requiring reconstructive management is low. Nonetheless, any technologies used in ureteric reconstruction after injury could also be potentially applied to the small number of cases of reconstruction following the treatment of ureteric disease.

The Clinical Approach to Ureteric Reconstruction

Managing Ureteric Injury

The approach taken to treat ureteric injuries is primarily dependent on the grade and location of the injury [2]. The first decision is whether intervention is required, and if so, whether surgery is the most appropriate treatment option. In cases of minor injuries and lacerations, surgery may not be required, and a ureteric stent may be more appropriate. However, if the damage to the ureter is more extensive, devitalised tissue is excised and reconstructive techniques become necessary. Various methods of reconstruction have been described, although there are limitations and risks of significant complications (Table 1) [9,36–39,44,46,48,49,77–83].

Ureteric Stents

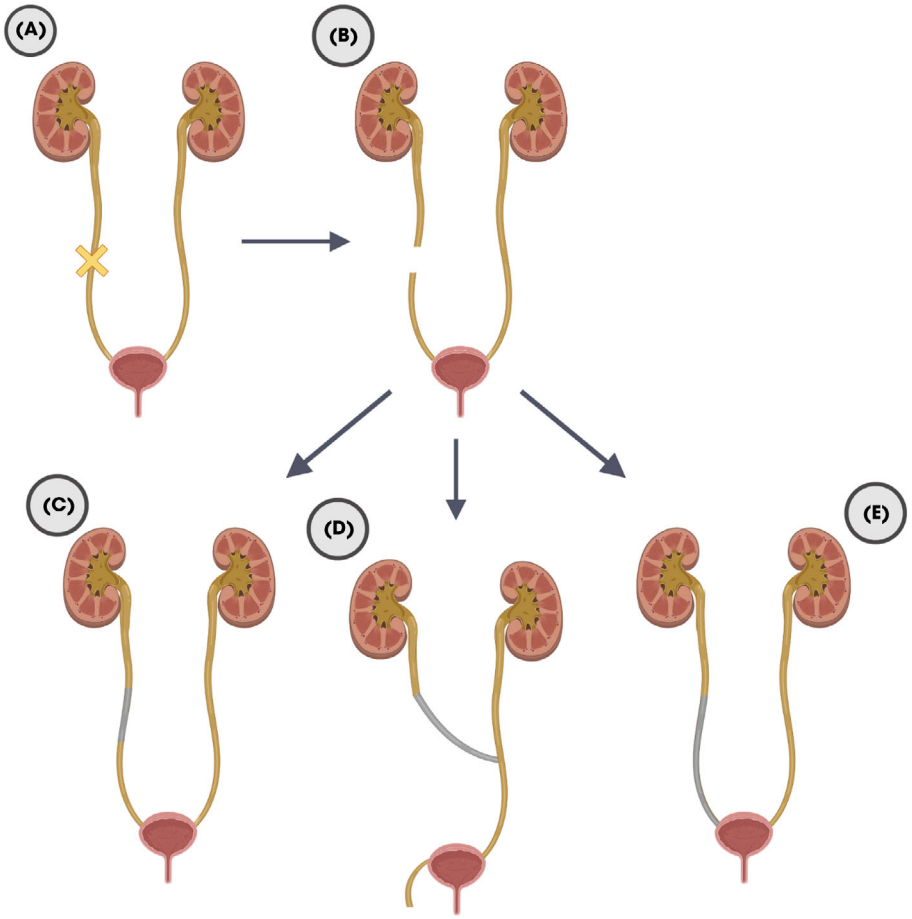
A key advantage of ureteric stents is that they can be inserted endoscopically or radiologically, thus avoiding the need for major surgical intervention. An injury of Grade I–III, as scored using the American Association for the Surgery of Trauma (AAST) classification, could be treated with a ureteric stent, which allows the ureter to heal over the stent and permit unobstructed urinary flow [2,30]. Stents are also commonly used in the management of external compression secondary to an abdominal tumour or retroperitoneal fibrosis. Although commonly used and generally effective, ureteric stents are mainly temporising measures and are associated with complications including pain and stent related

Table 1 Current standard of care for treatment of ureteric injuries.

Technique	Indication	Complication rate, %	Complications	References
Reconstruction using native urological tissue				
UU	Short (1–5 cm) ureteric injuries	0–10	Fistula, re-stricture, tissue necrosis, kidney mobilisation	[9,36,37]
TUU	Unilateral malignancy when other options are not available	0–40	Anastomotic haematoma, ureteric obstruction, ↓ renal function, stone development	[38,39,77]
UNC with PH and BF	Long (≤15 cm) ureteric segment damage	0–10	↓ renal function, dysuria, pain, UTI, superficial wound infection, malignancy recurrence	[36,78–80]
Reconstruction using GI tissue				
Ileal YM	Large (≤20 cm) ureteric defects - when native reconstruction is not possible	10–87.5	Metabolic acidosis, fistulae, anastomotic strictures, renal failure, urinary reflux, rupture of varicose vein within ileum, infection, hernia, fibrosis	[44,46,48,49,81]
Other GI tissue	Large (≤20 cm) ureteric defects when native reconstruction is not possible	29–87.5	Metabolic acidosis, fistulae, anastomotic strictures, fibrosis, UTIs	[81–83]

BF, Boari flap; GI, gastrointestinal; PH, psoas hitch.

Fig. 2 Surgical reconstruction of ureteric injury. The first surgical step is excision of affected tissue (**A** and **B**). Subsequently, depending on the site and location of the damage, either direct UU (**C**), or TUU (**D**), or UNC (**E**) are performed. UNC is usually performed with a Psoas hitch and/or Boari flap technique (not shown) when involving the distal segment of the ureter.



symptoms, an increased risk of infection, and encrustation [31,32]. Technologies under development that aim to reduce the risk of stent complications, include biodegradable polymer stents that can theoretically provide equal effectiveness in terms of maintenance of ureteric patency, whilst eliminating the risk of encrustation and reducing the susceptibility to bacterial adherence [33]. Moreover, polymer stents can be impregnated with medication, such as antibiotics or NSAIDs, to further limit the risk of complications whilst providing a more sophisticated treatment option for potentially inflammatory underlying pathologies (e.g., renal colic) [34,35]. However there is limited evidence for these options to be considered for standard practice.

Reconstruction Using Urinary Tract Tissue

Surgical reconstruction can be necessary when there is a significant loss of ureteric length. Ureteric strictures and ureteric injuries of <5–10 cm in length, can usually be reconstructed using urological tissue for reconstruction [36]. The three most common reconstructive approaches are: direct ureteroureterostomy (UU), transureteroureterostomy (TUU) or ureteroneocystostomy (UNC) (Fig. 2). UU refers to the primary anastomosis of the affected ureter and is used to manage short segment injuries and strictures [36], although there are concerns about the technical difficulty and the risk of ischaemia following UU reconstruction in the distal ureter [37,38]. In TUU, the affected ureter is joined to the contralateral, unaffected ureter. TUU is associated with potentially severe complications such as impaired renal function and urinary stone formation and is generally avoided if UU or UNC reconstruction is possible [39,40]. Lastly, UNC refers to the direct anastomosis of the ureter to the bladder. UNC is widely applied for short injuries (<5 cm) of the distal or pelvic ureter. For longer ureteric injuries (6–10 cm), more complex surgical techniques such as the psoas hitch or Boari flap or both in combination, are used [41].

These sophisticated approaches to ureteric reconstruction are associated with risks including formation of scar tissue and ureteric strictures, particularly at the site of anastomosis [42]. Extensive scarring is most likely associated with micro-trauma

to the vascular pedicle and is responsible for ~40% of ureteric-repair failures [11,43]. This highlights the need for the introduction of novel therapeutic approaches in the management of ureteric injury. Even technologies that aim to improve surgical precision, such as robotics, have to date failed to demonstrate any improvement in the outcome of ureteric reconstruction surgery [37,44].

Reconstruction Using Gastrointestinal Tissue

Reconstruction of ureter using gastrointestinal tissue may be considered when an injury is too extensive and severe to be managed by other means described above. Such injury is often the result of radiation therapy or iatrogenic damage [45]. Ileal replacement is currently the 'gold standard' approach for extensive ureteric reconstruction (>15 cm). Contraindications include intestinal pathologies such as inflammatory bowel disease [9]. The use of intestinal tissue is associated with risk of long-term complications including: (i) mucus production, (ii) urinary stone formation, (iii) stenosis, (iv) urinary reflux, (v) infection, (vi) nephritis, (vii) hydronephrosis, (viii) metabolic acidosis (mainly in the elderly population), and (ix) recurrence of the original obstruction [4,36]. The introduction of minimally invasive techniques in ileal replacement therapy has led to some improvements in postoperative pain and recovery but has had no beneficial effect on the risk of complications [46]. The most significant advancement in the field came from the introduction of the Yang-Monti technique (YM), which involves surgical manipulation of short segment(s) of ileum to create a longer vascularised tube before anastomosing it to the ureter. Advantages of the YM include flexibility in length of the applied implant, an effective anti-reflux mechanism, prevention of metabolic abnormalities, and reduced mucous production [47–50]. Despite the introduction of such techniques, the risk of severe postoperative complications is reported to be >85% [51]. Thus, major improvements in outcomes are yet to be achieved, reiterating the need for the exploration and introduction of novel bioengineering solutions.

Bioengineering; the State of the Art

The Application of Bioengineering

Traditional surgical approaches to ureteric reconstruction are naturally limited by anatomical and biological constraints. It may be reasoned, therefore, that current techniques have near-exhausted their potential in optimising outcomes, and that transformative improvements are more likely to emanate from the field of tissue engineering (TE) [11]. TE or bioengineering, refers to the application of engineering principles to create structures that improve or replace biological tissues and holds the promise of transforming the field of ureteric reconstruction [55]. There are three main considerations during the application of TE to ureteric reconstruction: (i) the scaffold, (ii) the cellular population seeded onto the scaffold, and (iii) the processing of the structure before engraftment. The properties of the scaffold are critical to achieve optimal integration, ensure structural integrity, and exhibit the right biomechanical properties. Potential scaffolds range from synthetic grafts (i.e., artificially made polymers) to decellularised natural grafts and natural-synthetic hybrids (Table 2) [52–67,59–61,64–68,84,85]. Other important considerations include whether the scaffold should be seeded before implantation, and if so, with which cell type. Finally, there is the option of pre-implanting seeded scaffolds in a heterotopic site, such as the omentum, to aid vascularisation before engraftment onto the ureter. The optimisation of these parameters is essential in creating a construct that can be successfully engrafted in continuity with the affected ureter, in a readily accessible way, whilst minimising the risk of complications.

Natural Grafts

The principal approach to the use of natural grafts in animal models is to utilise decellularised donor tissues to achieve ureteric reconstruction or diversion. Most published preclinical studies in ureteric TE have utilised decellularised natural grafts such as intestinal, vascular, or urinary tissue. Natural grafts tend to exhibit a high capacity for cell binding and growth, as well as the appropriate mechanical properties [8]. Gastrointestinal grafts are usually obtained from the intestinal submucosa and are decellularised to eliminate any donor epithelium. They are subsequently either implanted as acellular structures, or are seeded with a specific cell population, such as autologous bladder smooth muscle cells (SMCs) and urothelial cells (UCs). In preclinical dog and pig models, seeded grafts appear to be associated with better functional outcomes, especially if implanted onto the omentum before being anastomosed to the affected ureter [53,54]. Other natural scaffolds, such as bladder or vascular acellular matrices have demonstrated similar potential in rabbit models, especially when seeded with a population of SMCs and UCs (Box 1) [55–58]. However, despite the functional capacity exhibited by seeded natural grafts, they are associated with a range of severe complications, relating to the integrity of the scaffold and the fibrotic response to engraftment (Table 2). Although natural decellularised tissues represent a potentially attractive scaffold option in ureteric engineering, their susceptibility to structural complications has diverted focus away from natural grafts towards synthetic alternatives.

Synthetic and Hybrid Grafts

Synthetic scaffolds are artificial polymeric structures that are designed to replicate the functional properties of the native ureteric tissue and may be biodegradable or non-

Table 2 Key urological bioengineered studies.

Scaffold	Seeding	Latest model	Complication rate, %	Complications	References
Natural grafts					
GI	Acellular	Rat, dog	50–100	Fibrosis and occlusion, renal failure, hydronephrosis, peritonitis, urine leak in nearly all subjects	[52,84]
	Autologous bladder	Pig	100	Failure to recreate functional ureter	[53]
	Fibroblasts	Rat	66	Urine leak, inflammation	[84]
Ureter/bladder	Acellular	Dog	100	Fibrosis and occlusion, hydronephrosis, renal failure, postoperative death	[85]
	Smooth muscle and stem cells (pre-implanted)	Rabbit, dog	0–25	Scarring, hydronephrosis, death	[54,55]
Vascular ECM	ADSC: smooth muscle and urothelium (pre-implanted)	Rabbit	N/A	N/A	[56,57]
Synthetic grafts					
Biodegradable (PGA and PLGA)	Smooth muscle	Pig	N/A	N/A (in vitro study)	[61]
Non-biodegradable (PTFE, 8-F silastic)	Acellular	Dog	N/A	N/A (in vitro study)	[59,60]
Hybrid grafts					
Collagen	Acellular	Pig, goat	50–100	Constriction, hydronephrosis, graft shrinkage, stenosis, inflammation, fibrosis	[64,65]
Collagen and biodegradable polymer (PLA, PLLA)	Urothelium (pre-implanted)	Pig	<20	Inflammation, fibroblast deposition and tissue contraction	[66–68]

ECM, extracellular matrix; GI, gastrointestinal; PLA, polylactic acid; PLLA, poly-L-lactic acid.

Box 1

Liao et al. [58] - Construction of ureteric grafts by seeding bone marrow mesenchymal stem cells and SMCs into bladder acellular matrix.

Liao et al. [58] aimed to create functional tissue-engineered tubular grafts that could be used for reconstructing a 4-cm ureteric segment. A decellularised rabbit bladder matrix was used as a scaffold, which was seeded with either rabbit bone-marrow MSCs and SMCs or SMCs only (n = 10 rabbits/group). Both grafts were transplanted in the rabbits' omentum for 2 weeks before use for ureteric reconstruction. After reconstruction, the bioengineered grafts were left *in situ* for 16 weeks, and the outcomes were monitored using histology and intravenous urography. At 7 days after reconstruction, the MSCs could be identified as $CD29^{+}$ $CD44^{+}$ $CD90^{+}$ $CD34^{-}$, indicating appropriate differentiation. At 8 weeks after engraftment, a multi-layered urothelium was visualised with neovascularisation and smooth muscle bundling. No severe complications were observed in the experimental group. However, five rabbits in the control group died within 4 weeks, with post-mortem analysis revealing scar formation and hydronephrosis. This study supports the use of natural, decellularised scaffolds in ureteric reconstruction and highlights the importance of using an appropriate cellular population for seeding.

biodegradable [59]. Non-biodegradable materials, such as polytetrafluoroethylene (PTFE) polymers, are usually used as acellular tubular structures in ureteric reconstruction and are usually associated with poorer outcomes compared with biodegradable, seeded alternatives [60,61]. Biodegradable synthetic scaffolds use materials such as polyglycolic acid (PGA) and poly-di-lactide-co-glycolide (PLGA) polymers, which can provide a functional alternative to native ureteric tissue when seeded with SMCs [62]. To increase their capacity for integration and achieve optimum biochemical properties, synthetic scaffolds often incorporate biological components such as hyaluronic acid or type I collagen [63,64]. Such 'hybrid' scaffolds exhibit moderate results when used as acellular grafts, as demonstrated in both pig and goat models. Specifically, such acellular grafts appear to be prone to a range of complications including constriction of the neo-ureter, graft shrinkage, and hydronephrosis [65,66]. Promisingly, when biodegradable polymeric structures with collagen (type I) are seeded with a native UC population, they can exhibit a range of desirable properties including biocompatibility, functional viability, and morphological appropriateness. When trialled in mouse models, they formed ureteric structures that exhibited appropriate morphological, structural, and functional characteristics [67,68]. These findings were replicated when similar hybrid grafts were seeded with porcine bladder UCs and implanted in pig recipients, inducing the formation of functional neo-ureters, and permitting 80% survival rates (Box 2) [69]. These experiments provide the first step towards translating these findings into human studies. Furthermore, the potential of hybrid scaffolds, seeded with specialised UCs and SMCs has been realised in a clinical setting for other parts of the urinary tract, namely urethral and bladder reconstruction. In

Box 2
Geutjes et al. [72] – Tissue-engineered tubular construct for urinary diversion in a preclinical porcine model.

Geutjes et al. [72] used a hybrid scaffold, composed of bovine type I collagen and Vypro II synthetic polymer, to create functional ureteric conduits. A sample of 10 female Landrace pigs were obtained, and the hybrid scaffold structures were either seeded with UCs (six pigs) or directly implanted (four) as an incontinent urostomy. The outcomes were assessed radiologically, via a loopogram, and histologically, following a sample sacrifice at 10 weeks. Eight pigs survived all 10 weeks, whilst there was one unrelated death, and one death due to graft obstruction. Upon radiological analysis, a functional tubular graft was observed in the eight pigs that survived, withstanding up to 40 cmH_20 water pressure. Upon histological analysis, it was revealed that a urothelial monolayer had formed over both seeded and unseeded scaffolds, along with evidence of neovascularisation and a moderate immune response. Partial stenosis was observed in all surviving ureters, and the Vypro II component of the polymer had failed to bio-integrate fully. These data further support the potential application of alternative bioengineered solutions in the ureteric reconstruction and provides evidence for the application of synthetic, biodegradable, unseeded products that could potentially be provided off-the-shelf.

a cohort of five paediatric patients that needed complex urethral reconstruction, a biopsy was used to extract autologous specialised UCs and SMCs. These cells were cultured expanded and then seeded on PGA scaffolds. The seeded grafts were implanted and after 3 months were able to perform as functional neo-urethral units without complications [70]. These results were verified at a median follow-up of 71 months postoperatively [71]. A similar methodology was applied to a cohort of seven paediatric patients with myelomeningocele and high-pressure or poorly compliant bladders who required cystoplasty. Similar results were achieved up to 4 years of follow-up [72]. However, the use of buccal mucosa cells to seed natural scaffolds in urethral reconstruction did not have the same results and has met with several complications [73]. These studies provide proof-of-principle that effective urological bioengineering is possible. Nevertheless, there are important outstanding challenges to be resolved to ensure optimal function, utility, and an acceptable adverse effect profile.

The Future Promise of Ureteric Bioengineering

The Ideal Solution

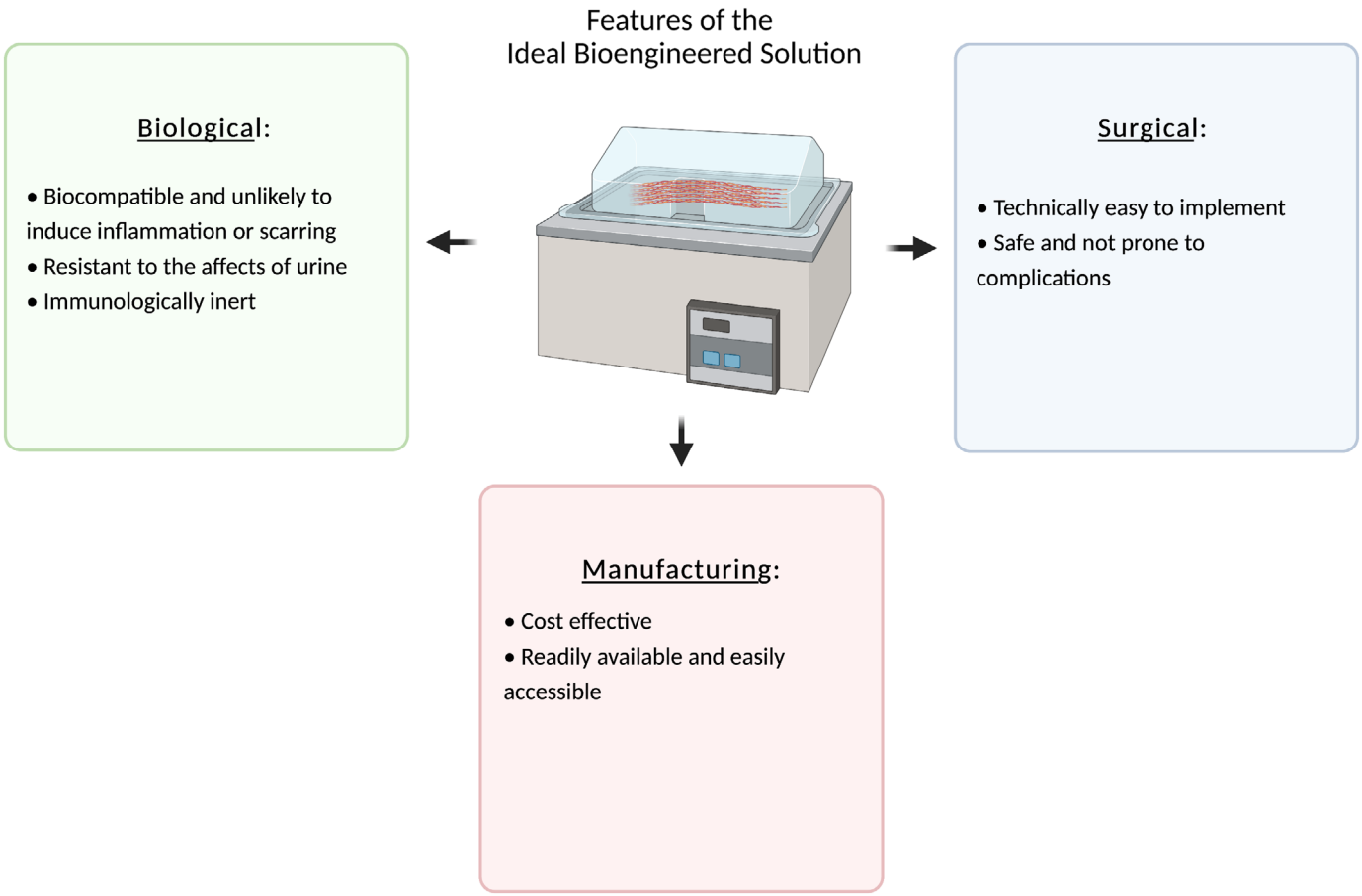
It is helpful to consider what properties an ideal bioengineered product should have in the context of ureteric bioengineering. We propose that such product should be: (i) biocompatible, so that it does not induce inflammation or fibrosis; (ii) resistant to the effects of urine to prevent leakage; (iii) safe and not prone to complications such as infections (including zoonosis) or cancer; (iv) surgically and technically easy to implement; (v) cost effective; (vi) readily available and accessible, ideally off-the-shelf, for large numbers of patients; and (vii) require minimal long-term management and immunosuppression (Fig. 3). It is thus important to compare and evaluate novel ideas and attempts for innovation against this ideal standard. Therefore, for every new solution that is conceptualised, there are several decisions to be made regarding which scaffold should be used and which seeded cell population offers the best chance of success.

Product Design

When designing the ideal ureteric bioengineered product, the first decision concerns the scaffold. Previous studies, summarised above, indicate that natural or hybrid grafts offer the greatest potential for creating a functional product [56,63,64]. There are three broad options for the cell type used for seeding the scaffold: (a) a stem cell population, (b) a differentiated primary urological cell population (e.g., smooth muscle and urothelium), and (c) a combination of the two. The use of stem cells in reconstructive medicine has long been realised [74], and in particular mesenchymal stromal cells (MSCs) and adipose-derived stem cells (ADSCs), have shown potential in ureteric reconstruction [55,58]. Specifically, there are several accounts of rabbit models of ureteric reconstruction, where either ADSCs or MSCs were seeded onto a bladder acellular matrix and pre-implanted in the omentum before use. The rabbit models have demonstrated the capacity of ADSCs and MSCs to differentiate into specialised UC and SMC populations, as well as their ability to form functional ureteric constructs [55,56,58]. An alternative approach that has demonstrated great potential is the use of endogenous precursor or specialised cells. Such cells are usually extracted by a biopsy and include UCs, SMCs, and chondrocytes [8]. The use of specialised UCs as the population of choice for seeding has been shown to be effective in both mouse and pig models, demonstrating good cell attachment, viability, and distribution, and permitting high survival rates [67,69]. The introduction of tissue-engineered autologous structures using specialised UCs and SMCs has also been successfully executed in a clinical setting for both urethral [70] and bladder [72] reconstruction. Further supporting this approach is the recent development by Sampaziotis et al. [75], who demonstrated the use of a similar concept using primary cholangiocytes seeded on a collagen graft, for biliary tract reconstruction.

The advantages and disadvantages of each method of ureteric bioengineering are described in Fig. 4. The balance of evidence suggests that an ideal product would incorporate the use of either a hybrid or natural graft scaffold, seeded with either specialised urothelium and/or an adult stem cell population, perhaps implanted in the omentum before being applied for ureteric reconstruction.

Fig. 3 Characteristics of the ideal bioengineered product. The ideal solution should be biologically compatible, easily, and cost-effectively manufactured, and technically easy to utilise.



Allogenic Versus Autologous Cells

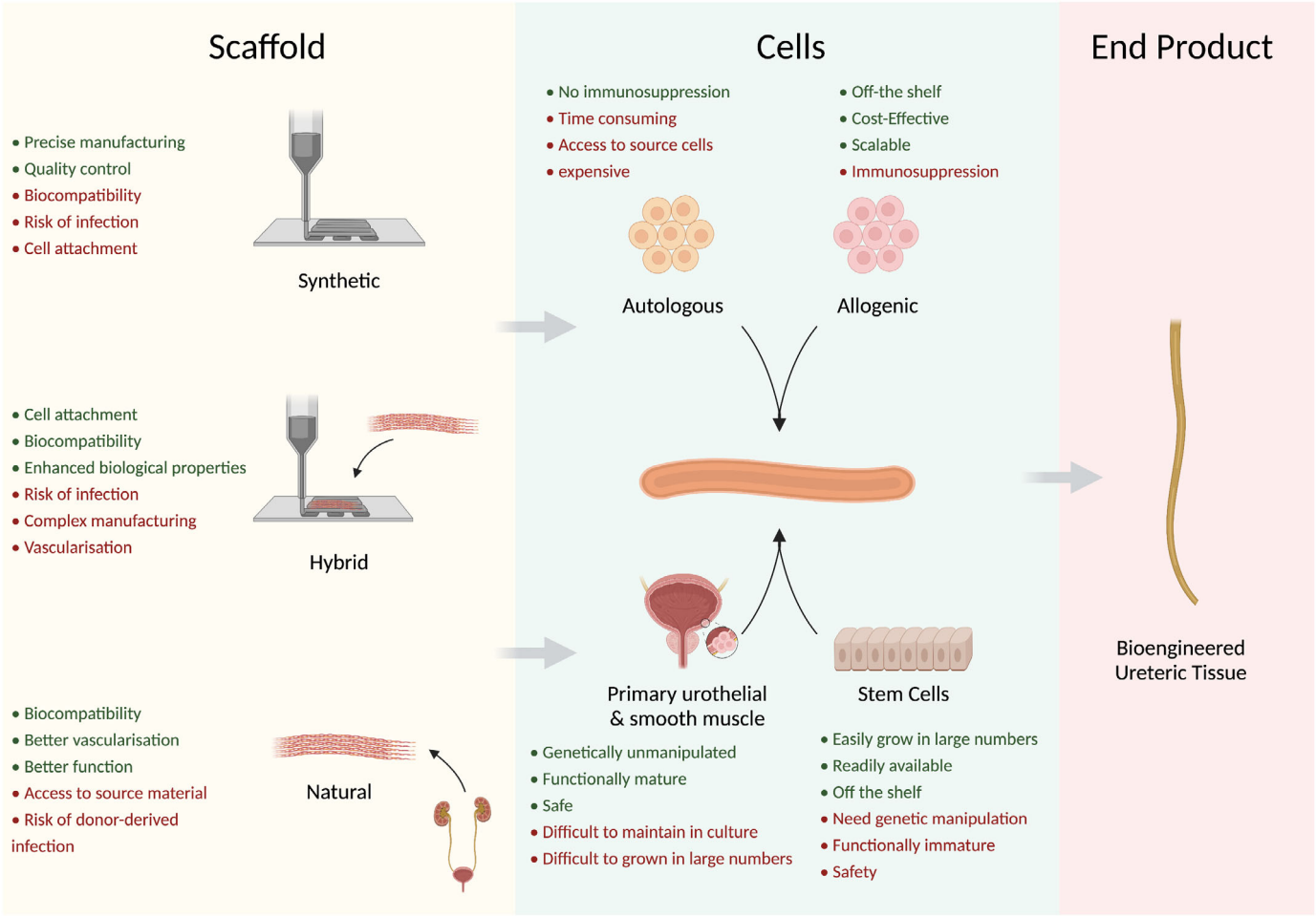
In addition to key decisions focused on the specialisation and type of the seeded population, an important consideration is whether autologous or allogenic cells should be used for TE. Use of autologous cells appears to be attractive as it theoretically eliminates the need for immunosuppression, and autologous urological tissue is relatively easy to extract by means of a bladder biopsy. However, the advantage offered by elimination of immunosuppression must be balanced against the increased time required to generate an autologous product, making the idea of an off-the-shelf product impossible. Moreover, it is likely that the cost of an autologous product would be prohibitively expensive for the foreseeable future. An allogenic product could conversely be produced and supplied off-the-shelf but would entail the likely risk of rejection without long-term immunosuppression, unless the scaffold is rapidly invaded by native cells, so that immunosuppression could be short term. To date, most preclinical models have used autologous constructs, as time and cost have not been key considerations (Table 2).

However, when translating these technologies into clinical products, time, availability, and cost become crucial. One way to eliminate the risk of rejection whilst using an allogeneic cell population is supressing the expression of human leucocyte antigen molecules, that are the dominant drivers of the immune response [76]. This has been successfully performed using human induced-pluripotent stem cells designed to be used as implants for cardiac repair, but as this technology is developed further, its applications would span throughout all fields of regenerative medicine [77,79].

Production and Delivery

Cost-effectiveness is a critical factor that will ultimately determine the feasibility of using a bioengineered product on a large scale and across all territories. This is inevitable as any new technology will be compared to the current standard of care, and the decision of whether it will be widely implemented in practice will be dependent in large part by health economics. Furthermore, for a bioengineered technology to be adopted in clinical practice, it needs to be

Fig. 4 Methods of construction of a ureteric bioengineered product. Synthetic, natural or hybrid scaffolds can be seeded with autologous or allogeneic cells that may be derived from stem cells or primary cells. The advantages and disadvantages of each approach are summarised in green and red text respectively.



easily deployable surgically, ideally requiring an intervention that is comparable to, or easier than, the current standard of care. Not surprisingly, technologies that pose a technical challenge may be met with resistance by surgeons and may have a high risk of complications stemming from the surgical procedure. Therefore, widespread clinical adoption of a novel product is dependent on cost and technical challenges compared to the standard of care it seeks to replace.

Methodology

A literature review was conducted in February 2021. Three databases were used in the literature search for this review: Google scholar, Medline, and Web of Science. Three different searches were conducted, investigating: (a) the epidemiology of ureteric disease and injury, (b) the current standard of care, and (c) the state of the art in ureteric bioengineering. Our search terms included: ('ureter' or 'ureteric' or 'ureteral') and either (a) ('injury' or 'disease') or (b) ('surgery' or 'surgical reconstruction', or 'reconstruction', or 'replacement', or 'standard of care'), or (c) ('bioengineering' or 'engineer*', or 'tissue engineering', or 'implant'), respectively for each of the three searches. Relevant studies were selected and analysed using an Excel spreadsheet. All data were then utilised in the construction of the manuscript.

Conclusion

Ureteric damage is a significant pathology with a risk of loss of renal function and poses several therapeutic challenges. Most common causes of ureteric damage are iatrogenic. Current management approaches, utilising urinary tract tissue or bowel for reconstruction, appear to be effective for repair of small, localised ureteric defects. However, existing techniques including ileal replacement, appear suboptimal for reconstruction of larger (>10 cm) lesions. TE approaches are a promising solution to this unmet need. Based on preclinical studies, the use of hybrid scaffolds, seeded with specialised

urological tissue, pre-implanted in the omentum before implantation onto the ureter, offers a particularly attractive option. However, more research is required before the potential of such bioengineering approaches is realised. The provided description of the ideal product should function as a reference guide to optimising novel techniques.

Conflicts of Interest

The authors declare no conflicts of interest.

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Correspondence: Kasra Saeb-Parsy, Department of Urology, Cambridge University Hospitals NHS Foundation Trust, Hills Road, Cambridge, CB2 0QQ, UK.

e-mail: kasra@doctors.org.uk

Kourosh Saeb-Parsy, Department of Surgery, University of Cambridge and Cambridge NIHR Biomedical Research Centre, Hills Road, Cambridge, CB2 0QQ, UK.

e-mail: ks10014@cam.ac.uk

Abbreviations: ADSC, adipose-derived stem cell; MSC, mesenchymal stem cell; PLGA, poly-di-lactide-co-glycolide; PGA, polyglycolic acid; PTFE, polytetrafluoroethylene; SMC, smooth muscle cell; TE, tissue engineering; TUU, transureteroureterostomy; UC, urothelial cell; UNC, ureteroneocystostomy; UU, ureteroureterostomy; YM, Yang-Monti technique.

