REVIEW

Biofabrication and biomaterials for urinary tract reconstruction

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Abstract: Reconstructive urologists are constantly facing diverse and complex pathologies that require structural and functional restoration of urinary organs. There is always a demand for a biocompatible material to repair or substitute the urinary tract instead of using patient's autologous tissues with its associated morbidity. Biomimetic approaches are tissue-engineering tactics aiming to tailor the material physical and biological properties to behave physiologically similar to the urinary system. This review highlights the different strategies to mimic urinary tissues including modifications in structure, surface chemistry, and cellular response of a range of biological and synthetic materials. The article also outlines the measures to minimize infectious complications, which might lead to graft failure. Relevant experimental and preclinical studies are discussed, as well as promising biomimetic approaches such as three-dimensional bioprinting.

Keywords: reconstruction, biofunctionalization, tissue engineering, urinary tract

Introduction

Reconstructive urology is a subspecialty dealing with repair, restoration, and replacement of parts or all of an organ of the urinary system.[1,2] Reconstructive surgeons are continuously searching for an ultimate biocompatible material, which when needed can substitute segments of urinary tracts in preference to patient's own tissues. As urologists always implement novel diagnostic techniques and therapeutic procedures to the field,[3,4] tissue engineering became the up-to-date area of research especially to those involved with reconstructive procedures.

Autologous tissues, such as intestinal segments, skin, and oral mucosa, are the current substitutes for reconstruction.[5,6] Nevertheless, there are numerous local and systemic complications associated with harvesting those tissues. The complications are clearly outlined in Table 1. Although tissue transfer techniques have been innovated throughout the years, aiming to reach the highest possible level of functional success, the reconstructive armamentarium requires an "off the shelf tissue" to limit patient's morbidity. Modernization of reconstructive urology recently involved the introduction of minimally invasive surgeries such as endoscopic, laparoscopic, and robotic procedures. This realistically decreased patient morbidity, enhanced postoperative recovery, and improved cosmetic outcome.[7] Nevertheless, despite this "high technology",[8] the functional outcome is rather similar to conventional surgeries. Using a "substitute" that physiologically behaves similar to urinary tissues will provide a practical solution to complex and recurrent cases, which are considered challenging even to experts.

The aim of this study was to highlight how biomimetic approaches are implemented in order to address the unmet needs in developing a bioengineered material that can

Table 1 Contemporary reconstructive approaches for management of different urinary tract pathologies

Hollow urinary tract organs	The commonest pathologies	Gold standard reconstructive techniques	Autologous non-urinary tissues	Limitations of autologous tissues
Urethra	1. Urethral stricture[165] 2. Complicated hypospadias[166,168]	Urethroplasty[168–171]	1. Oral mucosal grafts (buccal and lingual)[172,173] 2. Local skin flaps and skin grafts[173]	Oral mucosal grafts[174,176] 1. Donor site morbidity 2. Pain, bleeding, and infection 3. Parotid duct injury 4. Graft contracture 5. Oral numbness
Urinary bladder	1. Bladder cancer 2. Neurogenic bladder dysfunction 3. Detrusor overactivity 4. Chronic inflammations and granulomas[177]	1. Radical cystectomy and urinary diversion[178] 2. Augmentation or substitution cystoplasty[179,181]	Intestinal segments[181,183]	Intestine[176] 1. Metabolic disturbances 2. Renal function deterioration 3. Bacteriuria 4. Mucous overproduction 5. Stones 6. Perforation 7. VUR 8. Carcinoma
Ureter	1. Iatrogenic injuries 2. Ureteric strictures 3. Ureteric tumors	Depending on the anatomical part (upper, middle, and lower) and the extent of damage:[184] 1. Ureteroureterostomy 2. Transureteroureterostomy 3. Ureterocalycostomy 4. Boari flap 5. Psoas hitch 6. Autotransplantation 7. Ileal substitution	Intestinal segments[23,185]	

Abbreviation: VUR, esicoureteral reflux.

stand as a future graft for urinary tract reconstruction. This study specially focuses on the fabrication techniques as well as the biofunctionalization strategies, which form the platform technology for regenerating urological tissues. The physiochemical and biological properties of materials can be tailor-made to match those of the urinary tract. The three elements of urinary tract regeneration are the cells, the scaffolds, and the physiological environment for tissue growth and survival. Classically, the approaches involve either cell-based therapy alone or implantation of a biomatrix whether or not seeded with cells.[9]

Properties of an ideal biomaterial for urinary tract substitution

Broadly speaking, bioengineered tissues must be biocompatible, biodegradable, and well vascularized.[10,11] Regenerated urinary tract tissues should be characterized by unique physical and biological properties to match the physiological functions of urine storage and emptying.[12,13] Previous studies, as in bladder tissue engineering, showed that the biodegradation process reflects tissue remodeling. Eventually, if the degradation process follows the rate of regeneration within a suitable timeframe, this will result in a terminally differentiated functional urothelium.[14] Moreover, the material has to support adequate smooth muscle regeneration. This is best accomplished by seeding the scaffold with smooth muscle

cells.[15] Achieving an appropriately thick muscular layer will allow the regenerated tissue to be robust, withstanding rupture if overfilled with urine. It is also of equivalent importance for effective contractions.

Structural integrity and mechanical stability are both necessary for surgical handling of tissues, as well as to avoid diverticulum formation when subjected to extreme voiding pressures. Although strength is imperative, the material must also be compliant to accommodate increasing volumes of urine during the bladder storage phase without generating high pressures.[16] Compliance could be adjusted by tailoring the mechanical properties of the material to simply stretch. This pliability is also critical for urethral reconstruction, in order to anastomose it freely with native tissues in a water-tight fashion, ensuring a good blood supply. This is vital in penile urethral substitution, where shearing of the material could result from stress forces of erections.[17]

Unquestionably, the material must be completely impermeable to urine, as urine is cytotoxic to the growing cells and urine leakage can subsequently lead to a devastating urinoma.[18] Furthermore, the surface of the material in contact with urine should resist the formation of bacterial biofilms and encrustations, avoiding long-term complications on the upper urinary tract.[13]

Table 2 and Figure 1 summarize the ideal properties for biomaterials substituting urinary tissues.

Table 2 Summary of the properties of the ideal biomaterial for urinary tract reconstruction

General properties	Urinary-specific properties
1. Biocompatible	1. Stretchable
2. Biodegradable	2. Shape memory (regains its shape)
3. Promotes vascular and nerve regeneration	3. Soft
4. Promotes cellular differentiation	4. Watertight
5. Not toxic to the cells	5. Resists encrustations
6. Not carcinogenic	6. Resists biofilm formation
7. Unlimited supply	
8. Cost-effective	
9. Tailor-made physical and mechanical properties	
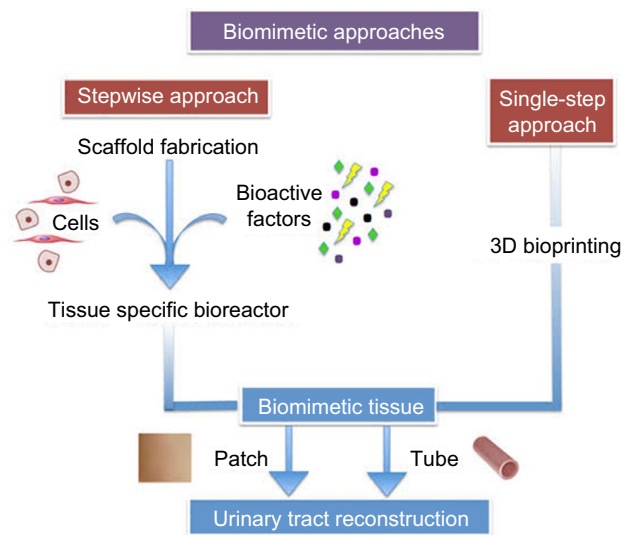
Figure 1 Approaches for biomaterial fabrication.
Note: This figure illustrates the different approaches for fabrication of biomaterials.
Abbreviation: 3D, three-dimensional.

Biomaterials for urothelium regeneration

Biomatrix acts as a supporting backbone for tissue regeneration maintaining its structural stability and allowing its growth in a three-dimensional (3D) manner. Moreover, it should incite cellular interaction and differentiation. Biomaterials in the history of urology started with the development of urethral catheters.[13] They are generally classified according to their source of origin into biological, synthetic, and hybrids of both. They can also be classified according to their degradation property into biodegradable and nonbiodegradable. Lastly, they can either be cell-seeded or non-cell-seeded.[19]

Biofabrication of the urinary tract

Important experimental and clinical applications will be discussed later in the section of biomimetic strategies.

Biological scaffolds
Natural polymers

Natural polymers such as collagen, alginate, and gelatin are mechanically weak. It is challenging to alter their mechanical properties. Therefore, their biomedical use is usually restricted as adjuncts to other materials. Nonetheless, they have shown their usefulness as inks in tissue bioprinting.[20,21] Chitosan, on the other hand, is an advantageous polymer as it is positively charged. This positive charge is useful for the immobilization of other negatively charged polymers such as gelatin and collagen as well as some growth factors. This immobilization property can aid in controlling the stability of the regenerative process.[22]

Biological scaffolds such as bladder acellular matrix (BAM),[23–27] small intestinal submucosa (SIS),[28,29] acellular amniotic membrane,[30] and acellular corpus spongiosum (ACSM)[31] have been previously experimented primarily because they mimic the native extracellular matrix (ECM). However, research is still ongoing to optimize their use for urological reconstruction.[32] They also harbor various growth factors and structural proteins such as glycosaminoglycan, collagen type 1, and elastin. Therefore, their mechanical properties are almost matching with those of the innate tracts. A study[34] that involved testing the mechanical behaviors of SIS, BAM, ACSM, and polyglycolic acid (PGA), comparing them to rabbit urethra as control, showed that there was no significant difference in terms of Young's modulus or stress at break between the SIS and BAM grafts. However, when it tested a four-layer graft, it showed better properties than one-layer graft ($P<0.05$). Therefore, it was concluded that SIS or BAM had higher strain-at-break measurements than ACSM and PGA (97.83%, 93.33% vs 53.30%, 39.70%), which were closer to normal rabbit urethra (173.67%).[33]

In vivo studies demonstrated evident growth of urothelium and smooth muscle cells over areas of defect when using cell-seeded biological scaffolds. In the non-cell-seeded approach, smooth muscle regeneration did not exceed 30% of the scaffold surface area. Hence, it was deemed unsuitable for long defects.[15]

Acellular scaffolds have inherent limitations, most importantly their potential of eliciting cytotoxic immune reactions. This could be explained by the presence of residual cellular elements that remain even after extensive decellularization. Subsequently, the resulting fibrosis will complicate the implantation process. Also, the long processing time, together with the limited supply of these materials, further emphasizes that they are not the best option for urinary tract substitution. Although extremely rare, a risk of infection with prion viruses might occur, specifically from materials of xenogeneic origin, such as porcine SIS.[17]

Silk fibroin (SF)

SF is naturally derived from *Bombyx mori* cocoons. It is an evolving material for use in urinary reconstructive procedures. It has excellent inherent biocompatibility with less immunogenic and inflammatory reactions, compared to other biological materials. The mechanical properties are superior in terms of elasticity and stability of its shape.[34] SF can also be electrospinned turning it to a highly porous scaffold. This unique feature is desired for cell-seeded approaches. Seeding SF with diverse cell types was successful in various preclinical urological studies.[35–39] Electrospinned SF showed perfect biological and mechanical tissue performance when used in augmenting the bladder of a rabbit model. It was efficient at generating functional smooth muscle regeneration compared to BAM.[40]

Electrospinned SF was also useful in promoting nerve regeneration. Nerve guidance conduits made from silk fibroin and poly(lactic-*co*-glycolic acid (PLGA) through electrospinning and weaving were able to promote and maintain Schwan cell growth in vivo in rabbits.[41] This could be applied in the near future as a biomaterial to promote nerve tissue regeneration for bladder or ureteric engineering. The aim was to have a functional tissue for bladder contractions or ureteric peristalsis.

In a recent urethral study,[39] acellular bilayered silk fibroin was used as an onlay patch in a rabbit urethral model. It was capable of supporting urethral regeneration similar to conventional SIS scaffolds, but with much less immunogenicity.[39]

Synthetic polymers

Synthetic polymers include polycaprolactone (PCL), polylactic acid (PLA), PGA, PLGA, and polyurethane (PU). Since their Food and Drug Administration (FDA) approval, they were extensively tested in various areas of biomedicine.[11]

They have myriads of advantages, making them theoretically superior for urinary tract applications. Their supply is limitless. Furthermore, porosity, ultrastructure and surface area to volume, elasticity, and degradation can be well handled to match the original tissues. Nevertheless, synthetic polymers do lack biological recognition. Unlike biological materials, they do not possess inherent growth factors and proteins mandatory for cellular interactions.[19]

Biofabrication of the urinary tract

ECM consists of various proteins, most importantly collagen, elastin, and glycosaminoglycan, ligands, and growth factors. They provide the structural support and tensile strength, as well as cellular adhesions and signaling.[42,43]

Mimicking urinary ECM can be achieved by modifying and assembling the biomatrix structure at the micro or nano scale. This changes its physical and biological behaviors to adapt to the urinary environment.

Strategies to match the physical properties

Hybrid biomaterials

Combining synthetic and naturally derived or natural biomaterials to manufacture a hybrid material is well known for utilizing the desirable properties of each. Biological scaffolds as BAM will enhance the stretchability of the graft, as it is rich in collagen type 4. Synthetic polymers, on the other hand, will maintain the mainframe structure of the tissue. A contemporary limitation in blending different materials is the difference in their structure chemistry. However, chemical modifications to conjugate them together were successful but potentially altered their biological behavior. Manufacturing techniques, such as electrospinning, have been successful in mechanically stabilizing hybrid polymers, which in turn supported the growth of different cell types. Electrospinned PLGA fibers were efficaciously mixed with BAM to support the growth and differentiation of bladder smooth muscle cells.[44] In an experimental study involving,[45] a hybrid material composed of equal amounts of PLGA and chitosan showed similar mechanical results to SIS controls. Moreover, canine smooth muscle viability was superior to the controls.[45]

Modifiable scaffolds

Recently, nanostructured titanium dioxide (TiO_2) scaffolds were tested as new nanocomposites for possible urological applications. TiO_2 scaffolds of different shapes such as tubes, wires, spheres, and porous membranes resulted in a terminally differentiated multilayered urothelium 3 weeks after seeding with porcine urothelial cells. These results highlighted their ability to adapt to different contours without changing their biocompatibility. TiO_2 scaffolds represent a good nominee for future widespread applications in urinary reconstruction.[46]

Strategies to match the biological properties

Topographical modifications

Surface roughness

The surface topography of scaffolds is crucial for cellular growth and differentiation.[47,48] Synthetic nanocomposites possess the advantage of tailoring their structure at the nano and submicron scales. Increasing polymer surface roughness improves its attachment to cellular proteins, a necessary affair

for urothelial cell adhesion.[47] Poly-carbonate-urea-urethane was treated in an experimental study[50] to increase its surface roughness by adding carbon nanotubes. This resulted in an increased adsorption of fibronectin without altering the surface chemistry of the polymer.[49]

An alternative approach to modify material roughness is chemical modification of the polymer fibers by alkaline hydrolysis. This modification also improves polymer biocompatibility.[50] However, chemical etching using sodium hydroxide hydrolysis is associated with change in the chemical composition and architectural orientation of synthetic polymer fibers. Therefore, the mechanical properties will change accordingly.[50,51] For that reason, additive manufacturing (AM), which will be discussed in the next section, has the advantage of controlling the material surface roughness without chemical processing. In a recent bone tissue-engineering study,[52] AM-guided 3D selective laser melting of the polymer has produced the optimal surface roughness for cell adhesion. The material morphology and visual observations were assessed using scanning electron microscopy and 3D micro computed tomography (CT).[52]

Pore geometry

A morphological feature of utmost importance for cell seeding is pore geometry. Optimum pore size, number, and interconnectivity are essential for the regenerating tissues to endure. The presence of pores provides a pathway for the diffusion of nutrients to the cells as well as for the elimination of unnecessary metabolic wastes.[53,54] Cellular attachment and proliferation require pore sizes ranging between 100 and 400 μm and should involve at least 75% of the scaffold surface area.[55] Various methods were described in the literature to produce a 3D porous scaffold. Conventional fabrication techniques for porosity of the scaffold such as salt leaching, gas forming, phase separation, and freeze-drying cannot control the microarchitecture of the scaffold. This issue could be solved using a computer-assisted AM approach.[56]

Relation between surface topography and stone deposition

A chief concern for using synthetic polymers in urological reconstruction is their exposure to urine, as the bladder is the main reservoir of urine. Therefore, the urine transit time is at its maximum. In some metabolic conditions, such as hypercalcuria and oxaluria, the calcium and oxalate crystal supersaturation permits nucleation of stone crystals. Consequently, it was imperative to study the relation between the topography of scaffolds and stone deposition. Chun et al[58]

studied the effects of nano-rough surface and the presence of submicron pores of PLGA and PU polymers on both urothelial cell adhesion and calcium oxalate deposition. An increased urothelial cell density was evident in the highly porous scaffold compared to nonporous ones. In addition, higher amounts of both calcium and oxalate crystals were deposited into submicron pores of the nano-rough PU inhibiting its crystallization in solution. The amount of calcium adsorbed on the submicron PU pores was four times higher than that on conventional PU. The authors concluded that submicron porous nano-rough PU prevented calcium oxalate crystal nucleation and formation.[57]

Influence of fabrication techniques on scaffold topography

Conventional methods

Several classic assembly techniques aim to modify synthetic polymer fibers for optimum cell anchoring, which include electrospinning (ES), thermally induced phase separation, self-assembly, and wet spinning. ES is the most widely used technique. Unfortunately, it lays down smaller fibers with haphazardly arranged pores, not in favor of cell penetration. However, the morphology can be better optimized when ES is combined with other techniques like AM.[58]

AM

Unlike conventional techniques, AM-3D printing-rapid prototyping controls scaffold microarchitecture with greatest precision.[59] AM builds scaffold layers from ground level. It also uses a variety of raw materials to customize the scaffold architecture. The process is assisted with the aid of a computer software (computer-aided design [CAD]) for prototyping models aiming to mimic the original structure of the tissue or organ. Implementation of computer-designed models to direct scaffold fabrication is referred to as computer-assisted tissue engineering. It is a groundbreaking tool recently introduced to biomaterial designing technology. Several AM methods are available now on the market, which include fused deposition modeling, selective laser sintering, stereolithography, precision extrusion deposition, and 3D printing.[60,61]

Hybrid AM combines AM techniques with conventional methods, most commonly ES. It aims to integrate materials at the assembly or technique levels and, accordingly, gain a dual benefit.[62] Hybrid AM in the field of bone and cartilage tissue engineering successfully manufactured 3D hierarchical structures with high porosity.[63–66] Subsequently, it was extended even further to involve the field of soft tissue engineering such as skin, vascular, and nerve regeneration.[67–69]

Although AM approaches are superior in designing and optimizing polymer architecture, the range of suitable biomaterials available for processing is limited with respect to soft tissue engineering. For example, hydrogels are attractive materials for soft tissues, but their processing and maintaining their 3D integrity are challenging with several AM techniques.[70]

Incorporation of bioactive molecules into the scaffold

Several studies used exogenous trophic factors to biofunctionalize scaffolds, particularly in bladder tissue engineering.[71–73] Bioactive factors are categorized into 1) natural ECM proteins (GAGs) such as collagen, laminin, and fibronectin; 2) short peptide sequences such as RGD and YIGSR; 3) growth factors such as vascular endothelial growth factor (VEGF), insulin-like growth factor 1 (IGF-1), basic fibroblast growth factor (bFGF) , platelet-derived growth factor (PDGF), and hyaluronic acid (HA); and 4) synthetic molecules. Loading scaffolds with bioactive agents creates a microenvironment simulating ECM. This environment allows cells to grow, interact, and differentiate into complex tissues, specifically urothelial, smooth muscle, vascular, and nerve tissues.[74,76] Bioactive molecules can be incorporated into the bulk of the polymer either during synthesis or by surface conjugation.

Growth factors

Basic fibroblast growth factor (bFGF) was chemically crosslinked to BAM to control its release. FGF promoted human fibroblast proliferation after implantation to a rat bladder reconstruction model.[76] The PLGA nanoparticles were used as delivery agents loaded with HA to modify porcine SIS scaffolds for bladder augmentation in Beagle dogs. In that study, full thickness regeneration was noted in all canine models.[77] Recently, a study[77] used PLGA-loaded nanoparticles to deliver VEGF onto BAM to augment bladder in rabbits. The microvessel density in the experimental group was significantly higher compared to the controls. Moreover, shrinkage of the graft decreased by 27%.[78]

IGF-1 enhances smooth muscle regeneration. A recombinant variant was immobilized within the polymerization process of a 3D fibrin matrix. This was effective in inducing smooth muscle proliferation both in vitro and in vivo.[79] VEGF is also a growth molecule that recruits and enhances proliferation and survival of endothelial cells, promoting vasculogenesis.[80] VEGF was delivered on its own or combined with other growth molecules to miscellaneous scaffolds for

bladder augmentation in animal models. The histological outcome was appealing in terms of enhanced vessel, nerve, urothelial, and smooth muscle cell regeneration. The functional outcome was also promising as there was a marked increase in bladder capacity and compliance.[78,81–83]

Combining different recombinant growth factors produces a positive synergistic effect on bladder tissue regeneration. Yang et al[83] compared in vitro the biological effects of eight different growth factors on proliferation, migration, and wound healing of three cells. The results indicated that PDGF, epidermal growth factor, and VEGF were the most exciting growth factors for improving human bladder smooth muscle, urothelial, and vascular endothelial cell activities. Those findings proposed their potential use for bladder regeneration and angiogenesis.[84] Sharma et al[85] bioactivated the elastomer poly(1, 8-octanediol-co-citrate) films (POCfs) with heparan sulfate, generating a heparin-binding POCf (HBPOCf), subsequently liberating proangiogenic factors such as VEGF, FGF2, and IGF-1 from HBPOCf. The in vitro analysis, after ~1 month, demonstrated topographical modifications together with a threefold increase in vessel density compared to the controls. The in vivo studies were conducted after subcutaneous implantation of the biofuntionalized scaffolds (HBPOCf-VEGF) within the dorsa of nude rats. Angiogenesis was further confirmed by CD31 and VWF immunostaining of the implanted sites.[85]

Short-sequence peptides

Short-sequence peptides such as RGD and YIGSR are used in regenerative medicine.[86] They act by attaching the cytoskeleton by integrins to the ECM immobilizing them, allowing better adhesion and growth.[87] RGD-modified PLGA scaffolds demonstrate a better smooth muscle cell adhesion compared with unmodified ones.[88]

Influence of surface chemistry on cell–biomaterial interaction

Modifying the material surface biochemistry can render it receptive for cellular attachment.[89] Hydrophilic surfaces are preferred for better interaction with urothelial cells, which is achieved by adding functional groups onto the polymer surface. Various chemical and physical methods were used to treat the polymers in order to achieve this goal.

Uchida et al[89] described layer-by-layer (LbL) modification of poly(carbonate urethane) urea (PCUU) scaffold surface by adding fibronectin and gelatin layers. The modified scaffold surfaces demonstrated higher affinity with urothelial and bladder smooth muscle cells compared to uncoated PCUU.[90]

Garcia-Garcia et al[91] treated the surface of poly(3-hydroxybutyrate-co-3-hydroxyvalerate) by sodium hydroxide hydrolysis. It resulted in functionalization of the polymer with -NH$_2$ and -COOH groups. Covalent attachment of the YIGSR sequence increased the hydrophilicity of the polymer surface, resulting in improved adhesion and growth of porcine urothelium.[91] The same group expanded their work further on a different polymer, poly(3-hydroxybutyrate-*co*-3-hydroxyhexanoate), using sodium hydroxide hydrolysis and ethylenediamine aminolysis in aqueous and isopropanol media.[92]

One of the main advantages of plasma gas treatment of polymers is the introduction of functional groups to its surface. However, there is a concern of changing their physiochemical properties.[93,94] Pandiyaraj et al[94] used plasma-treated thin transparent TiO$_2$ film coated on the surface of a flexible poly(ethylene terephthalate) film. It resulted in increased hydrophilicity by adding a negatively charged group, as well as increased surface roughness. This adjustment was not cytotoxic to the cultured osteoblasts. Of interest, an antibacterial activity against *Staphylococcus* group of bacteria was noted.[95]

Ultraviolet cross-linking technology uses the same principle as plasma. Although it has been the focus of several vascular and cardiac tissue-engineering studies,[96–98] several biocompatibility and mechanical issues limited its use for soft tissue engineering.[99]

The role of cell seeding and cell–scaffold interaction
Autologous cells
Urothelial cells are attractive for cellularizing biomatrices for bladder and urethral reconstruction. As they are autologous, there is a low risk of inducing autoimmune reactions.[100] Moreover, their isolation, as well as their method of culture, is well established and described liberally in the literature.[101,102] However, their use may not be proper in some diseases.[103] Also, harvesting cells from patients with urothelial carcinomas carries the risk of tumor recurrence.[104] Moreover, Subramaniam et al highlighted that urothelial cells derived from bladders with neuromuscular dysfunction revealed poor regenerative capability when cultured in vitro.[105]

Another alternative autologous epithelial cell that is under focus of research is tissue-engineered buccal mucosa. It is showing promising results in preclinical and clinical trials for future implication as an alternative cell source for urethral tissue engineering.[35,106,107] In a recent clinical study involving 12 patients, stricture recurrence in the anterior urethra occurred in two patients only.[108] However, researchers should extend the follow-up period to include a higher number of patients and consider different stricture etiologies for further trials.

Stem cells (SCs)
SC application in reconstructive urology is unveiling hopeful results.[109] Adult mesenchymal stem cells (MSCs) are more favorable than fetal SCs because they are not associated with teratoma formation, nor the ethical dilemma surrounding them.[110] They are harvested from different sources (eg, bone marrow, adipose tissue, and skeletal muscles). They have an exquisite pluripotentiality to differentiate into multiple cell lineages, including osteoblasts, chondrocytes, myocytes, adipocytes, and neurons.[111] Adipose-derived stem cells (ADSCs) are one of the most promising cells for urological tissue engineering, mainly due to their high abundance in and their simple isolation from patients.[112]

Urine-derived stem cells (UDSCs), similar to MSCs, have the pluripotentiality to differentiate into several tissue types, including urinary structures. They do not necessitate aggressive techniques for sampling and are cost-effective. They also have an immune regulatory function as well as angiogenic properties.[113] Both MSCs and UDSCs exhibit paracrine effects by secreting various cytokines and growth factors such as hepatocyte growth factor, nerve growth factor (NGF), glial growth factor, IGF-1, and VEGF. The paracrine effects of SCs play a major role in tissue regeneration by exhibiting both antifibrotic and angiogenic effects.[114]

Induced pluripotent stem cells (IPSCs) are genetically bred SCs and are generated from somatic cells by inducing the expression of different transcription factors. They could offer several advantages over the adult SCs while maintaining the plasticity of embryonic SCs.[109] They have a marvelous self-regenerative ability and also can differentiate into diverse cell lineages. They were reported successfully for the first time for their use in prostate, bladder, and ureter regenerative applications by reprograming stromal cells into an embryonic SC-like pluripotent state.[115]

The functional aspect of the regenerated tissues, especially the urinary bladder, should not be underestimated. As previously mentioned, the most important function of the bladder is to effectively contract and empty urine. This requires proper smooth muscle and nerve regeneration. Detrusor muscle is the major functional tissue of the bladder, but has to be well innervated by sympathetic and parasympathetic nerve supply. This enables the bladder to coordinate its storage and emptying.[109,116] UDSCs and MSCs have both shown in numerous studies that they are a well-established source for detrusor muscle engineering, and exhibit phenotyping features similar to bladder smooth muscle cells.[117–120] A recent study involving ADSCs with a BAM graft showed an enhanced detrusor muscle, neuronal regeneration, and

increased bladder capacity in a rat bladder model.[24] This indicates that ADSCs are very promising in bladder regeneration.[24] Biofunctionalized scaffolds with NGFs and MSCs were effective in promoting nerve regeneration in bladder TE.[116,121] Further strategies for the functional aspects will be discussed later in the section of promising strategies.

Antimicrobial surface properties
Urological diseases necessitating reconstruction, such as urethral stricture and neurogenic bladders, are chronic in nature and are associated with urine stasis. Frequently, they are complicated by urinary tract infections,[122] which are usually polymicrobial and multidrug resistant.[123–125] Similar to urethral catheters and ureteric stents, colonization with virulent uropathogens on the inner surface of biomaterials forms a sturdy biofilm resistant to the action of standard antibiotics and disinfectants.[126,127] Urea-splitting bacteria, particularly *Proteus* species, can deposit encrustations on the synthetic material surface.[128–131] Those encrustations can theoretically block the lumen of tubularized synthetic scaffolds. For that reason, antibiofilm modifications are essential preventive strategies to maintain the patency of synthetic tubular grafts. Nanostructured surfaces may influence the behavior of bacteria on the surface of biomaterials.[132] Bacterial adherence and biofilm formation onto these surfaces vary widely according to the biological properties of the species and the nano-topographical features of the surface.[133,134]

Noble metals
Noble metals such as silver and gold have excellent inherent properties for antimicrobial applications. Biocompatibility, hydrophobicity, and slow development of resistant strains make them the best surface agents for long-term use in the urinary tract. Nevertheless, their cost-effectiveness, biodistribution profile, and possible systemic toxicities need to be addressed for future lifelong use in urinary reconstruction.[135]

An experimental study involved surface functionalization of nylon catheters by coating them with a 100 nm layer of silver nitrate.[136] A sustained release of silver particles was observed at the implantation sites over 10 days. This modification prevented the biofilm formation of various gram-positive and gram-negative bacterial uropathogens, as well as *Candida* species. The in vivo analysis in male mice revealed that the biodistribution of silver was stable. Only 20% accumulated locally in the implantation site with <1% systemic organ distribution.[137] Also, functional gold nanoparticles effectively suppressed the growth of multidrug-resistant uropathogens in vitro.[136]

Nitric oxide (NO) donors
NO is known to have an antibacterial activity by suppressing bacterial adhesion and causing dispersion of the attached biofilms.[138,139] Slow release of NO can be accomplished by surface impregnation of NO donors into synthetic polymers. A novel study by Colletta et al[139] tested the possibility of using S-nitroso-N-acetylpenicillamine (SNAP)-impregnated silicone Foley catheters for the prevention of catheter-associated urinary tract infections (CAUTIs). SNAP is a synthetic NO donor able to generate NO at stable levels.[141] It is also able to suppress the formation of biofilms of two well-known microorganisms triggering CAUTIs and urinary device infections, *Proteus mirabilis* and *Staphylococcus epidermidis*.[140]

Promising strategies
Tissue/organ engineering is undergoing a major shift. Smart biomaterials and organ bioprinting are promising research areas for biomedical applications. They can overcome the current limitations of materials used in soft tissue and complex organ reconstruction.

Smart polymers
Smart or stimulus-responsive biomaterials sense the changes in microenvironments, such as the pH, temperature, or mechanical stimuli, and consequently respond by changing their properties.[142,143] In general, smart biomaterials that are clinically relevant and currently used for some medical applications are smart hydrogels, shape-memory polymers (SMPs), and stimulus-responsive nanoparticles.

SMPs are implemented in various medical applications such as devices for minimally invasive surgery, the delivery of therapeutics, and scaffolds for tissue engineering.[144] The earliest application of SMPs in urology was their integration in stents with thermo-expandable shape-memory properties. The stents were used to circumvent many ureteric, urethral, and prostatic gland diseases.[145,146] Regarding regenerative medicine applications, SMPs were experimented in various vascular and bone tissue engineering/regenerative medicine studies.[147–149] Their biocompatibility with cells and their tailored mechanical properties are promising. SMPs can respond to different stimuli by changing their shapes and dimensions; subsequently, on removal of the stimulus, they can regain their original shape.[150] For that reason, it is relevant to explore the concept in response to urinary stimuli. In bladder reconstruction, these polymers can be tailored to change their shape in response to bladder filling, urine pH, or temperature and subsequently regain back their original shape after emptying. For urethral applications, if used as implants in the penile

urethra, they can stretch with penile erections, and then can shrink back to their original shape after detumescence.

Electroconductive polymers are also an interesting subset of smart polymers and can be very beneficial for bladder tissue regeneration. Electroactive PU polymers have shown great potentials for Schwan cell regeneration and muscle cell expression. This could help growth of detrusor and bladder nerve regeneration for effective contractions. This might be further maintained by a sort of electromagnetic stimulation.[116,151–154] Electroconductive natural polymer-based hydrogels can compatibly be suitable for bladder bioprinting.[155]

3D bioprinting

Tissue bioprinting involves direct printing of living tissues in a 3D manner in order to produce a complex structure simulating the original organs. Unlike other AM methods, it involves incorporation of cells, growth factors, and biomaterials simultaneously in a one-step approach.[156] Recently, Kang et al[156] reported a novel 3D bioprinting system able to fabricate human-scale tissue constructs of any shape. The integrated tissue–organ printer (ITOP) is a smart technology that involves the integration of medical imaging data from CT or magnetic resonance imaging scans to a computer software. The software analyses the anatomical defects, translating them to a 3D CAD model. A visualized motion program controls the bioprinter nozzles to dispense cell-laden hydrogels within specific areas of biodegradable polymers, such as PCL. This technique controlled several tissue microarchitectures in a precise manner resulting in uniform pore geometry. The ITOP system successfully printed the calvarial bone, ear cartilage, and skeletal muscles. Cell viability was not affected by the printing process when tested using sensitive assays. It is expected that this technology will soon be long-drawn-out to print more complex tissues and organs.[157]

Another group[157] used a computer-aided four-headed 3D printing system to design and print heterogeneous tissue/organ constructs. The system used cell-laden hydrogels and thermoplastic polymers such as PCL, PLA, and PLGA. The algorithm using the multiple-head tissue/organ building system (MtoBS) is an LbL process that is able to lay down two or more kinds of cells per gel solution. Products were well integrated mimicking original tissues both internally and externally. It was able to print external ear, kidney, and tooth with diverse tissue components.[158] In another study,[159] the 3D bioprinters utilized decellularized ECM bioinks to print tissue analogs. This technique was versatile. Different tissues such as cartilage, heart, and adipose were successfully printed. The tissue constructs demonstrated prolonged stability and cellular compatibility in all experimental assays.[159]

The earliest application of 3D printing in the field of urology was for tissue simulation as a surgical education tool. It was also used for prototyping cancer models for correlation between imaging and histology in prostate and renal cancers.[160–163] A recent study by Zhang et al,[164] which is considered the first, described 3D bioprinting of the urethra. This group succeeded in using the previously mentioned ITOP system to bioprint a composite urethral scaffold. It consisted of a PCL/PLCL-blended porous spiral scaffold together with two types of autologous cells (rabbit bladder urothelial and smooth muscle cells) dispensed in fibrin hydrogel of which a thorough in vitro assessment of the biomimetic mechanical properties and cell growth environment was carried out. The results of the study revealed that the biomaterial mechanical properties were equivalent to native rabbit urethra. Cell viability and proliferation were maintained sufficiently in the hydrogel. This study provided a strong foundation for future studies on 3D bioprinting of the urethra but has to be tested first in animal models.[164]

Although tissue bioprinting appears ideal for tissue/organ reconstruction, its use is still experimental. The limited supply of materials, non-optimized mechanical properties, infrequent preclinical studies, time consumption, and high cost restrict its current use in laboratory research.[156,165]

Conclusion and future directions

The ultimate goal of reconstruction of urinary organs is not only anatomical but also functional. They are hollow, are elastic, and can be seeded with the similar cell types. The bladder is the most sophisticated to mimic, structurally and dynamically. On the other hand, the urethra, ureters, and neo-conduits are geometrically simpler to refashion as tubes.

Despite the enthusiasm and achievements so far, there is no "ideal biomaterial" available yet. Modification of biomaterial nanostructure will enhance its biological properties for cellular integration. Accordingly, successful tissue remodeling will be achieved. Smart polymers need to be explored even further to optimize their use in urinary reconstruction. They can be custom-made to change their shape and response when contacting urine. 3D bioprinting can further integrate sophisticated imaging techniques such as optical coherence tomography (OCT). OCT should be able to scan the depth of tissues on the ultra-molecular scale.

Overall, the field of tissue engineering is growing fast, implementing modern machinery to achieve its goal. The future might reveal definitive time-saving solutions, for example, intraoperative scanning of tissue defects with a "real time 3D bioprinting" using autologous tissues to reconstruct the diseased segments.

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Disclosure

The authors report no conflicts of interest in this work.

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