World Journal of Urology (2020) 38:2081–2093
https://doi.org/10.1007/s00345-019-02833-4

TOPIC PAPER

Review of clinical experience on biomaterials and tissue engineering of urinary bladder

Michael E. Chua[1,2] · Walid A. Farhat[3] · Jessica M. Ming[4] · Kurt A. McCammon[1]

Received: 1 April 2019 / Accepted: 30 May 2019 / Published online: 20 June 2019

Abstract

Purpose In recent pre-clinical studies, biomaterials and bladder tissue engineering have shown promising outcomes when addressing the need for bladder tissue replacement. To date, multiple clinical experiences have been reported. Herein, we aim to review and summarize the reported clinical experience of biomaterial usage and tissue engineering of the urinary bladder.

Methods A systematic literature search was performed on Feb 2019 to identify clinical reports on biomaterials for urinary bladder replacement or augmentation and clinical experiences with bladder tissue engineering. We identified and reviewed human studies using biomaterials and tissue-engineered bladder as bladder substitutes or augmentation implants. The studies were then summarized for each respective procedure indication, technique, follow-up period, outcome, and important findings of the studies.

Results An extensive literature search identified 25 studies of case reports and case series with a cumulative clinical experience of 222 patients. Various biomaterials and tissue-engineered bladder were used, including plastic/polyethylene mold, preserved dog bladder, gelatine sponge, Japanese paper with Nobecutane, lypholized human dura, bovine pericardium, amniotic membrane, small intestinal mucosa, and bladder tissue engineering with autologous cell-seeded biodegradable scaffolds. However, overall clinical experiences including the outcomes and safety reports were not satisfactory enough to replace enterocystoplasty.

Conclusion To date, several clinical experiences of biomaterials and tissue-engineered bladder have been reported; however, various studies have reported non-satisfactory outcomes. Further technological advancements and a better understanding is needed to advance bladder tissue engineering as a future promising management option for patients requiring bladder drainage.

Keywords Biomaterials · Bladder tissue engineering · Review · Clinical experience

Introduction

The bladder, despite its complex anatomic and physiological pathways, primarily serves as a reservoir to both store and empty the urine excreted from the kidneys. To repeatedly hold and empty urine to its appropriate capacity, it requires a repetitive mechanism of adequate relaxation and contraction with a unique lining to withstand intraluminal pressure and urine solution [1, 2]. The bladder has multiple layers including the inner epithelial lining that protects the underlying stroma from urine and multiple external layers of muscle fibers that coordinate with the external urethral sphincter to function appropriately in storage and voiding [3].

Several congenital and acquired bladder conditions (such as bladder exstrophy, neurogenic bladder, malignancies, and trauma) with anatomical or functional abnormalities require surgery to preserve renal function. Some necessitate either complete removal of the bladder and urinary diversion via conduit or augmentation to increase its storage capacity [4, 5]. To date, these procedures are traditionally performed using a segment of the gastrointestinal (GI) tract. However, the GI tract substitution is associated with local and systematic complications such as urine leak, malignancy, stone formation, and metabolic disturbances due to the different

✉ Kurt A. McCammon
McCammKa@evms.edu

[1] Eastern Virginia Medical School, Norfolk, VA, USA

[2] St. Luke's Medical Center, Quezon City, NCR, Philippines

[3] University of Toronto, Toronto, ON, Canada

[4] University of New Mexico, Albuquerque, NM, USA

absorptive and secretory properties of the intestinal tract [4–6]. Furthermore, the quality of life using the GI tract can be affected significantly due to its related morbidities and sequelae [6–10].

Bioengineering has been exploring an alternative approach to improve outcomes for these patients. Efforts focused on bladder tissue regeneration were initially carried out with experimental studies performed in vitro and in vivo using biomaterials with or without tissue-specific seeded cells. Biomaterials used in bladder tissue engineering are currently either biologic or synthetic scaffolds that serve as the solid support matrix for tissue regeneration [10]. The biologic scaffolds are either naturally derived or acellular tissues; while the synthetic scaffolds are either polymers or silk-based materials [10–12]. The approach of using biomaterials seeded with tissue-specific cells or a stem cell source have been studied due to the fact that acellular scaffolding has a higher chance of post-implant contracture and fibrosis [13–15]. Biomaterials with stem cells or patient's autologous tissue cultures have been investigated to avoid tissue fibrosis [13–15], and with the created neotissue from autologous stem cells, reduce the immune rejection as previously described with allogeneic cell source [16–18].

Research in animal models has shown the feasibility of bladder tissue engineering; however, most of these studies utilized healthy animals in which translational applicability is uncertain [19, 20]. Clinical application of biomaterials and bladder tissue engineering has been attempted and the reports are intriguing. To give an up-to-date overview of the clinical experience, the scope of this review is mainly focused on the clinical experience of biomaterials and bladder tissue engineering. Hence, we aim to present a summary of the feasibility and clinical outcomes of the biomaterial usage and tissue engineering application in bladder regeneration.

Methodology

A literature search was performed in PubMed on February 1, 2019, with the search strategy used: ("urinary bladder"[MeSH Terms] OR ("urinary"[All Fields] AND "bladder"[All Fields]) OR "urinary bladder"[All Fields] OR "bladder"[All Fields]) AND ("tissue engineering"[MeSH Terms] OR ("tissue"[All Fields] AND "engineering"[All Fields]) OR "tissue engineering"[All Fields]). We did not restrict identification of relevant studies to the English language; however, foreign language studies were only summarized and assessed according to the available English reports. Assessment of relevance was accomplished by reviewing abstracts and identifying clinical studies. Screening on the identified records was categorized into clinical studies, animal experiments, and review articles. Records of review papers were gathered for cross-referencing and identification of relevant clinical studies. Full-text articles were ordered and included for the summary of literature specifically focused on reports on bladder tissue engineering clinical experience. The studies with reported clinical experience were then summarized for the biomaterial used, number of patients involved, outcomes, and follow-ups. When multiple publications of clinical experience were identified, only the latest and or most complete data reported were included in the summary of the clinical experience.

Results

Out of 1113 retrieved records, after screening, there were 190 animal studies available and 25 clinical studies with 222 patients. Studies are mainly case reports and case series with the application of various biomaterials. Table 1 summarizes the details of clinical experiences on various biomaterials usages and tissue engineering in bladder regeneration.

Clinical experience on biomaterials (synthetics and natural) alone for bladder regeneration

In 1957, Bohne and Urwiller reported seven patients' clinical experience with a plastic mold used as a bladder matrix, which was implanted after cystectomy and then explanted after a few weeks. However, the result was disappointing with serious morbidities and all pseudo-bladders formed over the plastic mold eventually contracted over time [21]. Subsequent clinical reports using a plastic mold also described similar outcomes [22, 23]. Although these studies did not show a promising outcome, they found that, although urothelial tissue regenerates, the muscle fibers do not, which lead to eventual contraction and fibrosis of the formed tissues.

Preserved dog bladders anastomosed orthotopically to patient's after cystectomy was being reported by Tsuji et al. in 1963 and 1967. He described major morbidities in most patients [24, 25]. The same author group also reported using Gelatin sponge sutured to the bladder edge or urethra of patients' post-cystectomies. Similarly, the results were disappointing with all patient's developing bladder contractures needing a urinary diversion or tumor reoccurrence [25]. Orisaka et al. in 1970 then further modified the biomaterial using Gelatine sponge with Nobecutane, which is ethyl acetate and acrylic resin compound with tetra-methylthiuram disulfide acting as a sealant and bactericide [26]. They reported four out of five patients with satisfactory outcomes, although a later study reported that bladder calculi seem to be a common complication with this biomaterial [26]. Further modification of the biomaterial was reported by Taguchi et al. [27] and Fujita [28] using Japanese rice

Table 1 Details of clinical experiences on various biomaterials' usage and tissue engineering in bladder regeneration

References	Biomaterials	Procedure/technique	Indications	Number of patients	Follow-up period	Outcome	Remarks/complications
Bohne and Urwiller (1957) [21]	Plastic mold	Plastic mold in bladder-shaped implanted into the bladder and then explanted after several weeks	Bladder carcinoma (4), Interstitial cystitis (2), tuberculosis (1)	7	12 days–1.5 years	All cases failed, generated pseudo-bladder formed fibrotic tissue and eventually contracted overtime	3 mortality at the post-operative period. Other complications include vesicocutaneous fistula, vesicoureteral reflux, hydronephro-ureter and urinary infections
Portilla Sanchez et al. (1958) [22]	Plastic mold	Plastic mold ovoid in shape placed in the vesical neck, removed after 3 months	Bladder cancer, post-total cystectomy (1)	1	5 months	Voided freely every 3 h with slight small amount incontinence	Biopsy taken in the newly form bladder cavity showed transitional epithelium but no muscular fibers
Tsulukidze et al. (1964) [23]	Plastic mold	Polyethylene shell plate/high-pressure film implant into the pelvis after total cystectomy, daily wash with Colimycin of upper tract via catheter. Shell plate removed after 2 months	Bladder cancer (28)	28	Not disclosed	One patient mortality after second procedure and two patients need further bladder closure. None disclosure of other remaining patients	Some patient may require abdominal manual pressure to void, some may have reflux which need double voiding
Tsuji et al. (1963) [24]	Formalin Preserved dog bladder	Preserved bladder anastomosed to the native bladder edge or urethra, and then, the graft removed after few weeks	Contracted bladder (tuberculosis)	2	Not disclosed	Not fully satisfactory on both cases, bladder capacity not over 100 cc or no post-op improvement	Remarkable vesicoureteral reflux unchanged. Remained with nephrostomy tube as safety valve. Discussed that contracted bladder and nephrostomy tube may contribute to post-op contraction
Tsuji et al. (1967) [25]	Gelatin Sponge	Anastomosis of the graft material to the cut edge or urethra (graft spontaneously dissolve and discharge into the urine).	Bladder cancer post-partial cystectomy (2), post-total cystectomy (2)	4	1–8 months	All cases failed. Tumor recurrence, contracted bladder and need for urinary diversion	Maximum capacity only up to 80–100 cc. Complication of stricture of ureteral orifices, vesicoureteral reflux, urinary leakage/incontinence, and consequent need for diversion

Table 1 (continued)

References	Biomaterials	Procedure/technique	Indications	Number of patients	Follow-up period	Outcome	Remarks/complications
	Preserved bladder	Preserved bladder anastomosed to the native bladder edge or urethra, then removed after 2–3 weeks (graft may discharge into the bladder cavity)	Bladder cancer post-partial cystectomy (4), post-total cystectomy (6)	10	1 month–4 years?	1 with 4 year follow-up showed satisfactory bladder function with slight stress incontinence. Remaining other cases failed with 2 mortality post-op 1 month, 2 cases with tumor recurrence; other had bladder contracture needing urinary diversion	Maximum capacity only up to 30–70 cc. Complication of severe urinary incontinence and vesicoureteral reflux consequent need for diversion
Orikasa and Tsuji (1970) [26]	Gelatin Sponge + Nobecutane	Gelatin sponge graft with edge sprayed with nobecutane, sewed to native bladder cut edge. Bladder wall edge fixed to pelvic tissues	Tuberculous contracted bladder (4), congenital hour glass bladder (1)	5	9 months?	Described success 4 out of 5 cases 1 patient bladder capacity increased to 350 cc after 8 mo, another patient 200 cc after 9 months, 1 patient had scarred bladder	Unilateral hydronephroureter, urinary leakage, bladder scarring. Biopsy of the scarred bladder showed satisfactory epithelial and muscle regeneration. Another study cited 2 years follow-up showed calculus formation on edge [27]
Taguchi et al. (1977) [27]	Japanese paper + nobecutane	Sterilized Japanese paper sprayed with nobecutane then dried in repeated process, configured to cap and sutured either to inside or outside of the opened native bladder. Removed in 3–4 weeks transurethral in 1 piece	Small contracted bladder (tuberculosis, interstitial cystitis)	13	1 year 2 months to 5 years 6 months	11 patients with favorable result with post-op bladder capacity > 200, 2 without effect (interstitial cystitis) bladder capacity < 50	Discussed granulated tissue not covered with mucosa leaks out exudates and prone to infection, irrigation to prevent infection and systemic chemotherapy needs to be administered carefully
Fujita (1978) [28]	Japanese paper + nobecutane	Resin (Nobectane) sprayed thin paper reconstructed with urinary bladder, then removed transurethral after 4 weeks when paper slough into the regenerated bladder	Bladder cancer (3) or tuberculosis (contracted bladder) (1)	4	4 weeks–1 year	3 with satisfactory result (bladder capacity > 200 cc), 1 failed to regenerate and eventual colocystoplasty	Urinary leakage and vesicoureteral reflux

Table 1 (continued)

References	Biomaterials	Procedure/technique	Indications	Number of patients	Follow-up period	Outcome	Remarks/complications
Schmiedt et al. (1974) [29]	Lypholized human Dura	(Foreign language abstract with no details)	Bladder carcinoma s/p subtotal cystectomy	2	?	Both have good regeneration of bladder wall and sufficient capacity	No complications
Kelami (1975) [30]	Lypholized human Dura	Lypholized human dura patch covered unto the bladder defect/resected portion	contracted bladder sec to interstitial cystitis/radiation cystitis (6), and bladder carcinoma (28)	34	2–6 years	Bladder functional enlargement were achieved in 19, 10 failed. 5 loss to follow-up	Perforation reported with urinary leakage and peritonitis and recurrence of tumor. States histologic finding of no signs of fibrosis or contracture at 28 week follow-up, although no muscle tissue in new bladder wall
Günther et al. (1979) [31]	Lypholized human Dura	(Foreign language abstract with no details)	Bladder carcinoma	9	?	1 failed	Complication includes calculi formation and immunological reaction with contraction of dura
Selli et al. (1986) [32]	Lypholized human Dura	Lypholized human dura patch sutured to the bladder dome as described by Kelami [30]	Contracted bladder due to multiple bladder tumor resection	1	30 months	Tumor recurrence over the dura patch, patient underwent radical cystectomy	Case supports the concept that implantation of tumor cells is a factor in the recurrence of superficial bladder carcinoma
Kakimoto et al. (1989) [33]	Lypholized human Dura	(Foreign language abstract with no details)	Bladder carcinoma	10	2 months to 1 year and 3 months	Eight cases were in good clinical condition but one case was treated by TUR for recurrence of bladder tumor 1 year and 3 months after operation	In three cases, prolonged urine leak from the wound continued after operation, and in one case, temporal VUR was found without clinical significance
Romero Pérez et al. (1990) [34]	Lypholized human Dura	(Foreign language abstract with no details)	Bladder carcinoma	15	5 years	Determined survival rates	No operative death or post-operative complication are few

Table 1 (continued)

References	Biomaterials	Procedure/technique	Indications	Number of patients	Follow-up period	Outcome	Remarks/complications
Arikan et al. (1995) [35]	Lypholized human Dura	Dehydrated human dura (Tutoplast Dura Pfrimmer) rehydrated prior to use, sutured anastomosed to entire bladder wall in two layers for augmentation	Neurogenic bladder (spinal injury, myelomeningocele)	10	1 years	Overall good outcome with 7 doing fairly well with reasonable cystometric capacity (> 200), continent between CIC with no need for oxybutynin, 3 need 10–20 mg oxybutynin bladder capacity > 100 cc	No serious pre–post-operative complications. One patient with urinary leakage after removal of catheter, resolved in 7 days
Moon et al. (2011) [36]	Bovine Pericardium	Bovine pericardium used to repair the bladder defect after cystectomy	Enterovesical fistula	1	2.5 years	Bladder wall intact on last follow-up with no fistula formation	Vesicoureteral reflux and contracted bladder
Barski et al. (2015) [37]	Amniotic Membrane	Three layers of Amniotic membrane rehydrated and sutured to the bladder defect	Vesico-vaginal fistula	1	6 months	Favourable result, amniotic membrane graft merged with the surrounding bladder tissue at the margins but was still clearly demarcated with no signs of overgrowing urothelium or stroma. No leakage	No severe complications, no sign of graft rejection
Mansson and Harzmann (1988) [38]	Biocarbon (Carbon Polymer)	Biocarbon implanted as stoma prosthesis for urinary conduits and cutaneous ureterostomy with Dacron velour graft	Bladder exstrophy (1), Bladder or ureteral carcinoma 8), stoma stenosis (4)	13	2–86 month follow-up	Five patients were reported to have good outcome; however, four of them died (two patients died of MI and two patients died of malignancy), seven cases need explant of the device due to complications	Three main complication: infection around devise, urinary fistula (1) and ureteral stenosis (2). Encrustation of the device

Table 1 (continued)

References	Biomaterials	Procedure/technique	Indications	Number of patients	Follow-up period	Outcome	Remarks/complications
Atala et al. (2006) [39]	Collagen bladder acellular matrix seeded with urothelial and smooth muscle cell	Acellular matrix scaffold seeded with autologous source cell from patient then implanted to patient 78 weeks after engineered bladder. Bladder was reimplanted to patient without omental wrap (3), with omental wrap (1)	Neurogenic bladder (Myelomeningocele)	4	22–61 months	Modest increase in compliance and decrease in bladder capacity with one patient increased intravesical pressure	One patient with yeast UTI, 2 with persistent VUR. Patients with omental wrap approach had better outcome with increased volume, compliance as well as better dry intervals. Full-thickness biopsy showed all bladder tissue component tissue present.
	Composite collagen with polyglycolic acid seeded with urothelial and smooth muscle cells	Acellular matrix scaffold seeded with autologous source cell from patient then implanted to patient 7–8 weeks after engineered bladder. Bladder was reimplanted to patient with omental wrap (3)	Neurogenic bladder (Myelomeningocele)	3	22-61 months	All have better outcomes as described for patients with implantation involving omental wrap	Renal function remained stable
Joseph et al. (2014) [40] (NCT00419120)	Autologous cell-seeded biodegradable scaffold [polyglycolide/polyactide mesh (Tengion)]	Surgical implantation of the autologous cell-seeded scaffold (harvested 5–7 weeks lab grown mucosa and muscle cell). With complete coverage of omentum held in place with suture and Crosseal fibrin sealant	Neurogenic bladder sec to Spina bifida	11	36 months	Five patients need further augmentation, One patient content with condition and continent, Two patients incomplete work-up for follow-up. No improvement in other patients	Five patients with complications: bladder rupture (2), bowel obstruction (3), and pelvic abscess (1), which need further surgical procedure. All patient experience at least 1 UTI
Bivalacqua et al. (2018) (NCT01087697) [41]	Biodegradable PLGA scaffold seeded with autologous adipose-sourced smooth muscle cells (SMC) (neourinary conduit)	Ureteral anastomosis to the conduit and wrapped around omentum or peritoneum for blood supply	Bladder cancer post-radical cystectomy	8	6 weeks–16 months	2 mortality (cancer, MI); 6 neourinary conduit explanted	Stromal stenosis (3), neourinary conduit stricture (3), average NUC life span 250 days. Concluded focus on implantation technique to prevent stricture formation

Table 1 (continued)

References	Biomaterials	Procedure/technique	Indications	Number of patients	Follow-up period	Outcome	Remarks/complications
Tengion (2018) (NCT00512148) [42]	Autologous cell-seeded neobladder constructs (biodegradable PGA/PLGA matrix scaffold)	Tengion neobladder augment was surgically attached to the patient's existing bladder	Neurogenic bladder with spinal cord injury	7	24 months	No improvement in bladder compliance or capacity	Four patients with serious complication: small intestinal obstruction (1), post-procedural leak (3); 6/7 had UTI
Caione et al. (2012) [43]	Small intestinal submucosa	Four layered SIS (Surgisis, Cook Urological, USA) diamond shaped sewn to the cross-shaped bladder walls opening, correct orientation of SIS, suture line sprayed with 5 ml fibrin glue and covered with perivesical tissue or omental flap	Bladder exstrophy	5	2–3 years	Progressive increase in bladder volume, without compliance deterioration or immunological and urological complications; however, the obtained functional results only partially satisfying, increased bladder capacity not fully adequate to achieve urinary continence and imperfect morphology	Two afebrile UTI, no mucous, bladder stones, nor diverticula observed. Some patient evaluated may need future augmenting enterocystoplasty and bladder neck surgery
Schaefer et al. (2013) [44]	Small intestinal submucosa	SIS membrane graft four layered (Surgisis) sewn between the muscle and mucosal layer of the bladder wall opening at the dome. Water tight anastomosis with fibrin glue and Tachosil (Nycomed, Germany)	Cloacal exstrophy (1), spina bifida (2), bladder exstrophy (2), VUR with multiple surgeries (1)	6	4.6–33.5 months	Four patients with increased bladder volume, continent in 4 patients, (3 with CIC, and one no need for CIC). 2 not continent	Bladder stones (2) and bladder rupture (1). Concluded that SIS failed to substitute enterocystoplasty

Table 1 (continued)

References	Biomaterials	Procedure/technique	Indications	Number of patients	Follow-up period	Outcome	Remarks/complications
Zhang and Liao (2014) [45]	Small intestinal submucosa	SIS membrane graft four layered (Surgisis) strap shape, rehydrated, and sewn to the mucosal layer of the bladder wall opening with correct orientation. Water tight anastomosis with soft perivesical tissue and an omental flap coverage	Spinal cord injury (2), Myelomeningocele (6)	8	11–36 months	All patients had significant increased maximum bladder capacity, and a decrease in maximal detrusor pressure. 1 year follow-up hydronephrosis resolved in 3/7 patients, improved in 2/7 patients	Two patients had UTI when initiating CIC, no metabolic abnormalities, no mucus production, renal, or bladder calculi. Two patients with persistent reflux. Renal function preserved in all patients

paper (Tetrapanax papyrifer) with Nobecutane. Taguchi et al. had up to 5.5-year follow-up with favorable outcomes, most patients with a post-op bladder capacity of > 200 cc [27]. However, no subsequent follow-up studies were carried out with this biomaterial.

From 1974 to 1995, several various studies from different institutions described clinical experiences with the use of lypholized human dura patch as a biomaterial for bladder substitution among patients with bladder tumors and/or contracted bladders [29–35]. The majority of the studies reported post-operative reasonable bladder enlargement and no serious complications; however, urine leakage and tumor recurrence were common with the overall outcome determined to be not fully satisfactory.

Other natural biomaterials include Bovine pericardium and Amniotic membrane, both used as a bladder patch for repair of enterovesical or vesicovaginal fistula [36, 37]. Although the studies described that the bladder wall remained intact with no recurrence of fistula on the last follow-up, both showed contracture of the graft. Mansson et al. also described using a synthetic biocarbon (Carbon Polymer) as a stoma prosthesis implant for 13 patients with urinary conduit or cutaneous ureterostomy. However, four out of five patients reported to having good outcomes had died when the study was being reported. The remaining patients had the implant removed due to various complications [38].

In 2012–2014, three studies reported using porcine small intestinal submucosa, commercially available as (SIS [Oasis®], Cook Biotech). It is an acellular, native collagen-based extracellular matrix (ECM) of submucosal layer being used among patients with neurogenic or congenital myogenic bladders [43–45]. All studies have reported increased bladder volumes; however, functional outcomes were described to be only partially satisfactory, in which some authors have concluded that SIS cannot substitute the enterocystoplasty [43, 44].

Clinical experience on bladder tissue engineering (biomaterials seeded with autologous cells)

In 2006, Atala et al. reported their clinical experience of seven patients with myelomeningocele using collagen only or composite collagen, polyglycolic acid bladder acellular matrix seeded with autologous urothelial and muscle cells [39]. The study highlights the importance of using an autologous cell tissue source to avoid an adverse immune-response while including muscle tissue in the seeded cell to enhance the presence of all bladder tissue components, as seen in their full-thickness bladder biopsies. Furthermore, the importance of an omental wrap for vascular supply was described with better outcomes. However, another three studies sponsored by Tengion, the company for autologous cell-seeded polyglycolide/polylactide matric scaffold

(bankrupted in 2014), showed poor outcomes among all trials [40–42] with no bladder compliance or capacity improvement. When used as a conduit, all patients eventually needed explantation; as augmentation, severe complications such as bladder rupture, small bowel obstruction, and infections were reported.

Discussion

Regenerative medicine using tissue engineering technology has been given high expectations due to its rapid development with potential for revolutionary treatment strategies [46, 47]. Specifically, in the field of reconstructive urology, there is high demand for a tissue-engineered product to be used as urinary conduits or augment patches to eliminate the use of bowel as the replacement [48]. Reports from animal studies using tissue bioengineering for bladder substitutes seem to be promising [20, 49]; however, in our review of clinical studies to date, all have shown non-satisfactory results.

The clinical experience using biomaterials stand alone either natural source or synthetics have shown that native urothelial has the capability to regenerate; yet, the muscle fiber layers only develop into fibrotic tissue and leading to eventual contracture inability to function. Similarly, with scaffold seeded with autologous stem cells, adequate development of all layers may be seen in histological study; however, the functional capability as the bladder organ in toto was not achieved, considering that multiple aspect of its development was not taken into consideration. It is important to understand that the bladder biological function is not simply for storage. Behind its urothelial regenerative capability and frequent urine expulsion lies a complex and unique infrastructure. Hence, the complex function requires composite histology and anatomy (special urothelial lining, muscle and extracellular matrix ratio). It has the characteristic of impermeable lining with moderately dynamic muscular and richly vascularized organ with intricate innervation (Fig. 1) [3]. The fractional understanding of bladder with simplicity in functional assessment among the pre-clinical and clinical studies has led us to underestimate the bladder and assume rapid success in tissue engineering [49, 50].

A recent review by Adamowicz et al. summarizes the understanding of tissue engineering from pre-clinical experiments and gave important factors to consider for translational application of bladder tissue engineering include (a) generating a physiological mechanical property specific for the urinary system; (b) adequate pre-vascularity or capability for diffuse vascularization post-implantation to avoid necrosis of the graft; (c) antifibrosis and immunomodulating properties that avoid extensive local scarring; (d) neuronal network innervation of the graft with the capacity to generate/receive signal conduction; and an (e) ideal micro-environment to sustain healthy autologous cells with appropriate growth factors to ensure quality graft growth [11].

In principle, the biomaterial as scaffold matrix needs to be dynamic and yet to allow cells to grow into them [50]. Hence, they need to be permeable, but, when the scaffold or biomaterial is permeable, the regenerating cells from the native tissue will compete with urine seeping through the pores, causing fibrosis [51]. Therefore, it is a good strategy to consider to have the scaffold seeded with autologous cells prior to implantation, but, then, there should be a fast and effective blood vessels growth to sustain the viability of the seeded cells when implanted; otherwise, the cells will die and the pores will be leaking urine/then causes fibrosis [50–52]. A possible strategy that could work is to have the cell-seeded scaffolds implanted into a diverted bladder, while maintaining some robust method of nutrient delivery

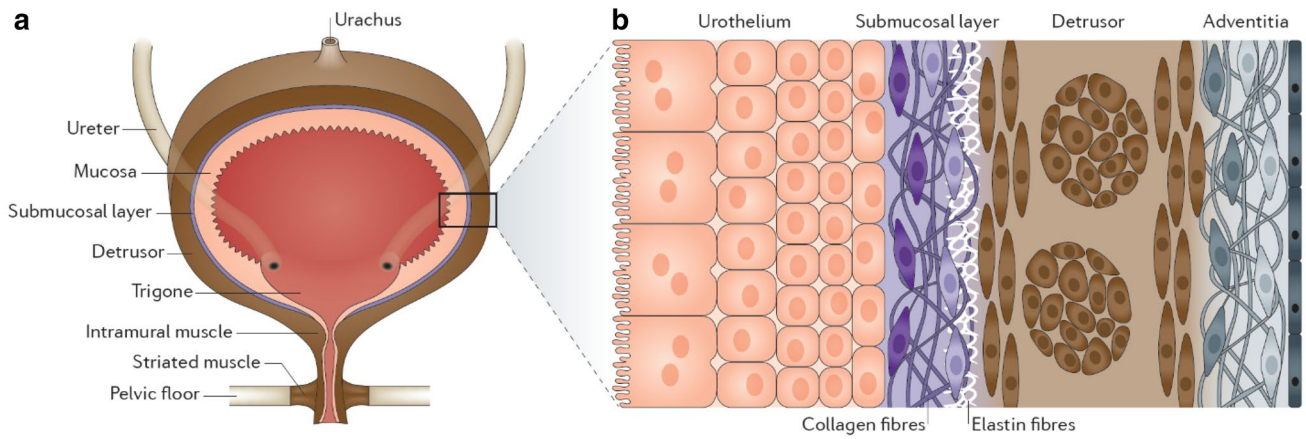

Fig. 1 Bladder structural anatomy and histologic characteristics. Adopted and reprinted by permission from Springer Nature: lic number 4,553,430,369,670 Ajallouеian et al. [49]

to the cell-seeded scaffold. Until the adequate angiogenesis occurred to supplement the cell-seeded scaffold with the necessary nutrients, then the bladder can be undiverted.

In general, the ideal engineered bladder needs to endure the urinary physiologic environment with the characteristics for supporting repeated storage and emptying of urine [53]. Addressing these complex and intricate processes requires more extensive research and advancements in technology; however, in the process of clinical studies, there need to have a both quality and safety of biomaterials in the human subjects [54]. To date, 3D-bioprinting, stem cell application, nanotechnology, and complex neuronal technologies are underway in pre-clinical phases [55–60], which should further advance the bladder tissue engineering experience.

Conclusion

The current clinical experience of bladder tissue engineering has not met a satisfactory outcome to replace enterocystoplasty. The main limitation was being due to the biomechanical characteristics of the urinary bladder and physiologic requirements to function optimally. Furthermore, issues regarding neovascularization and graft contraction due to immune-reaction or graft necrosis need to be addressed. Autologous cell-seeding and omental wrapping upon implantation seem to improve the clinical outcome; however, this is still not sufficient to endure long-term follow-up. While some of the clinical studies reported continence in a few patients, spontaneous voiding did not occur due to lack of neuronal networking as seen in a native bladder. Currently, technological advancements and scientific discoveries are underway to address these limitations and to advance bladder tissue engineering as a possible management option for patients needing a new bladder from oncologic, acquired, or congenital neurogenic and myogenic conditions.

Acknowledgements The author group would like to acknowledge the kind assistance of the library staffs from Edward E. Brickell Medical Sciences Library of Eastern Virginal Medical School in providing technical support and retrieving the full-text articles for the literature review of this paper.

Author's contribution statement MEC: project development, data Collection, data analysis, and manuscript writing. WAF: data collection, data analysis, and manuscript writing/editing. JMM: data analysis and manuscript writing/editing. KAM: project development, data collection, and manuscript writing/editing.

Compliance with ethical standards

Conflicts of interest Authors have nothing to disclose.

Research involving human participants and/or animals Not applicable for current article.

Informed consent Not applicable for current article.

References

1. Aitken KJ, Bägli DJ (2009) The bladder extracellular matrix. Part I: architecture, development and disease. Nat Rev Urol 6:596–611
2. Singh A, Bivalacqua TJ, Sopko N (2018) Urinary tissue engineering: challenges and opportunities. Sex Med Rev 6(1):35–44. https://doi.org/10.1016/j.sxmr.2017.08.004
3. Fry CH, Meng E, Young JS (2010) The physiological function of lower urinary tract smooth muscle. Auton Neurosci 154(1–2):3–13. https://doi.org/10.1016/j.autneu.2009.10.006
4. Stein R, Hohenfellner M, Pahernik S, Roth S, Thüroff JW, Rübben H (2012) Urinary diversion–approaches and consequences. Dtsch Arztebl Int 109(38):617–622. https://doi.org/10.3238/arztebl.2012.0617
5. Biers SM, Venn SN, Greenwell TJ (2012) The past, present and future of augmentation cystoplasty. BJU Int 109(9):1280–1293. https://doi.org/10.1111/j.1464-410X.2011.10650.x
6. Veeratterapillay R, Thorpe AC, Harding C (2013) Augmentation cystoplasty: contemporary indications, techniques and complications. Indian J Urol 29(4):322–327. https://doi.org/10.4103/0970-1591.120114
7. Huang Y, Pan X, Zhou Q, Huang H, Li L, Cui X, Wang G, Jizhong R, Yin L, Xu D, Hong Y (2015) Quality-of-life outcomes and unmet needs between ileal conduit and orthotopic ileal neobladder after radical cystectomy in a Chinese population: a 2-to-1 matched-pair analysis. BMC Urol 27(15):117. https://doi.org/10.1186/s12894-015-0113-7
8. Prcic A, Aganovic D, Hadziosmanovic O (2013) Impact of complications and bladder cancer stage on quality of life in patients with different types of urinary diversions. Med Arch 67(6):418–422. https://doi.org/10.5455/medarh.2013.67.418-422
9. Cho A, Lee SM, Noh JW, Choi DK, Lee Y, Cho ST, Kim KK, Lee YG, Lee YK (2017) Acid-base disorders after orthotopic bladder replacement: comparison of an ileal neobladder and an ileal conduit. Ren Fail 39(1):379–384. https://doi.org/10.1080/0886022X.2017.1287733
10. Serrano-Aroca Á, Vera-Donoso CD, Moreno-Manzano V (2018) Bioengineering approaches for bladder regeneration. Int J Mol Sci 19(6):1796. https://doi.org/10.3390/ijms19061796
11. Adamowicz J, Pokrywczynska M, Van Breda SV, Kloskowski T, Drewa T (2017) Concise review: tissue engineering of urinary bladder; we still have a long way to go? Stem Cells Transl Med 6(11):2033–2043. https://doi.org/10.1002/sctm.17-0101
12. Mahfouz W, Elsalmy S, Corcos J, Fayed AS (2013) Fundamentals of bladder tissue engineering. Afr J Urol 19(2):51–57
13. El-Assmy A, Hafez AT, El-Sherbiny MT, El-Hamid MA, Mohsen T, Nour EM, Bazeed M (2004) Use of single layer small intestinal submucosa for long segment ureteral replacement: a pilot study. J Urol 171(5):1939–1942
14. Wezel F, Southgate J, Thomas DFM (2011) Regenerative medicine and urology. BJU Int 108:1046–1065. https://doi.org/10.1111/1464-410X.2011.10206.x
15. Chung SY, Krivorov NP, Rausei V, Thomas L, Frantzen M, Landsittel D, Kang YM, Chon CH, Ng CS, Fuchs GJ (2005) Bladder reconstitution with bone marrow derived stem cells seeded on small intestinal submucosa improves morphological and molecular composition. J Urol 174(1):353–359
16. Zou Q, Fu Q (2018) Tissue engineering for urinary tract reconstruction and repair: progress and prospect in China. Asian J Urol 5(2):57–68. https://doi.org/10.1016/j.ajur.2017.06.010

17. Jayo MJ, Jain D, Wagner BJ, Bertram TA (2008) Early cellular and stromal responses in regeneration versus repair of a mammalian bladder using autologous cell and biodegradable scaffold technologies. J Urol 180:392–397
18. Xu Y, Sun DC, Wei ZT, Hong BF, Yang Y (2014) Experimental study on transplantation of autologous minced muscle with human umbilical cord mesenchymal stem cells for urethral reconstruction. Eur Rev Med Pharmacol Sci 18:3412–3419
19. Alberti C (2016) Whyever bladder tissue engineering clinical applications still remain unusual even though many intriguing technological advances have been reached? G Chir 37(1):6–12
20. Sloff M, Simaioforidis V, de Vries R, Oosterwijk E, Feitz W (2014) Tissue engineering of the bladder–reality or myth? A systematic review. J Urol 192(4):1035–1042. https://doi.org/10.1016/j.juro.2014.03.116
21. Bohne AW, Urwiller KL (1957) Experience with urinary bladder regeneration. J Urol 77(5):725–732
22. Portilla Sanchez R, Blanco FL, Santamarina A, Casals RJ, Mata J, Kaufman A (1958) Vesical regeneration in the human after total cystectomy and implantation of a plastic mould. Br J Urol 30:180–188
23. Tsulukidze A, Murvanidze D, Dvali R, Ivaschenko G (1964) Formation of a bladder by a plastic shell after total cystectomy. Br J Urol 36:102–105
24. Tsuji I, Kuroda K, Fujieda J, Shiraishi Y, Kassai T, Shida H (1963) A clinical and experimental study on cystoplasty not using the intestine. J Urol 89:214–225
25. Tsuji I, Kuroda K, Fujieda J, Shiraishi Y, Kunishima K (1967) Clinical experiences of bladder reconstruction using preserved bladder and gelatin sponge bladder in the case of bladder cancer. J Urol 98:91–92
26. Orikasa S, Tsuji I (1970) Enlargement of contracted bladder by use of gelatin sponge bladder. J Urol 104:107–110
27. Taguchi H, Ishizuka E, Saito K (1977) Cystoplasty by regeneration of the bladder. J Urol 118:752–756
28. Fujita K (1978) The use of resin-sprayed thin paper for urinary bladder regeneration. Invest Urol 15:355–357
29. Schmiedt E, Carl P, Staehler G, Wanner K (1974) Subtotal substitution of urinary bladder by a complete human dura of the skull cap (author's transl). Urologe A 13(5):228–231
30. Kelami A (1975) Duroplasty of the urinary bladder—results after two to six years. Eur Urol 1:178–181
31. Günther M, Pietruschka U, Siegel W, Erdmann T (1979) Use of the durain the surgical treatment of bladder cancer. Z Urol Nephrol 72:473–482
32. Selli C, Carcangiu ML, Carini M (1986) Bladder carcinoma arising from regenerated urothelium over lyophilized dura patch. Urology 27(1):53–55
33. Kakimoto S, Sakai H, Kubota S, Kondo A, Kishikawa M (1989) Partial cystectomy for bladder carcinoma: lyophilized human duraas a bladder wall substitute. Nihon Hinyokika Gakkai Zasshi 80:22–27
34. Romero Pérez P, Lobato Encinas J, Megía Carrigos J, Pelluch AA, Mira LA (1990) Partial parietal cystectomy and cystoplasty using alyophilized human dura mater patch as an alternative in palliative surgery for bladder cancer. Arch Esp Urol. 43:867–875
35. Arikan N, Ozdiler E, Yaman O, Go¨gu¨ s O (1995) Augmentation duracystoplasty in neurogenic bladder dysfunction. Int J Urol 2:172–175
36. Moon SJ, Kim DH, Jo JK, Chung JH, Lee JY, Park SY, Kim YT, Park HK, Choi HY, Moon HS (2011) Bladder reconstruction using bovine pericardium in a case of enterovesical fistula. Korean J Urol 52:150–153
37. Barski D, Gerullis H, Ecke T, Varga G, Boros M, Pintelon I, Timmermans JP, Winter A, Bagner JW, Otto T (2015) Repair of a vesico-vaginal fistula with amniotic membrane—step 1 of the IDEAL recommendations of surgical innovation. Cent Eur J Urol 68(4):459–461. https://doi.org/10.5173/ceju.2015.683
38. Mansson W, Harzmann R (1988) Clinical experience with an alloplasticstoma prosthesis (Biocarbon) for urinary conduits and cutaneousureterostomy. Scand J Urol Nephrol 22:223–226
39. Atala A, Bauer SB, Soker S, Yoo JJ, Retik AB (2006) Tissue-engineered autologous bladders for patients needing cystoplasty. Lancet 367:1241–1246
40. Joseph DB, Borer JG, De Filippo RE et al (2014) Autologous cell seeded biodegradable scaffold for augmentation cystoplasty: phase II study in children and adolescents with spina bifida. J Urol 191:1389–1394
41. Bivalacqua T, Steinberg G, Smith N, Joice G, Sopko N, Lerner S, Bochner B, Lee C, Rivera E, Jain D, Bertram T, Salem W, Schoenberg M (2018) Final results of a phase 1 clinical trial evaluating the use of a tissue engineered neo-urinary conduit using adipose derived smooth muscle cells for urinary reconstruction. J Urol 199(4S):e578
42. Tengion. NCT00512148. An open label multicenter study of augmentation cystoplasty using an autologous neo-bladder construct in subjects with neurogenic bladder following spinal cord injury. https://clinicaltrials.gov/ct2/show/NCT00512148. Accessed 20 Mar 2019
43. Caione P, Boldrini R, Salerno A, Nappo SG (2012) Bladder augmentation using acellular collagen biomatrix: a pilot experience in exstrophic patients. Pediatr Surg Int 28:421–428
44. Schaefer M, Kaiser A, Stehr M, Beyer HJ (2013) Bladder augmentation with small intestinal submucosa leads to unsatisfactory long-term results. J Pediatr Urol 9:878–883
45. Zhang F, Liao L (2014) Tissue engineered cystoplasty augmentation for treatment of neurogenic bladder using small intestinal submucosa: an exploratory study. J Urol 192:544–550
46. Del Gaudio C, Baiguera S, Ajalloueian F, Bianco A, Macchiarini P (2014) Are synthetic scaffolds suitable for the development of clinical tissue-engineered tubular organs? J Biomed Mater Res A 102(7):2427–2447. https://doi.org/10.1002/jbm.a.34883
47. Smolar J, Horst M, Sulser T, Eberli D (2018) Bladder regeneration through stem cell therapy. Expert Opin Biol Ther 18(5):525–544. https://doi.org/10.1080/14712598.2018.1439013
48. Serrano-Aroca Á, Vera-Donoso CD, Moreno-Manzano V (2018) Bioengineering approaches for bladder regeneration. Int J Mol Sci. https://doi.org/10.3390/ijms19061796
49. Ajalloueian F, Lemon G, Hilborn J, Chronakis IS, Fossum M (2018) Bladder biomechanics and the use of scaffolds for regenerative medicine in the urinary bladder. Nat Rev Urol 15(3):155–174. https://doi.org/10.1038/nrurol.2018.5
50. Farhat WA, Yeger H (2008) Does mechanical stimulation have any role in urinary bladder tissue engineering? World J Urol 26(4):301–305. https://doi.org/10.1007/s00345-008-0318-4
51. Farhat W, Chen J, Erdeljan P, Shemtov O, Courtman D, Khoury A, Yeger H (2003) Porosity of porcine bladder acellular matrix: impact of ACM thickness. J Biomed Mater Res A 67(3):970–974
52. Loai Y, Yeger H, Coz C, Antoon R, Islam SS, Moore K, Farhat WA (2010) Bladder tissue engineering: tissue regeneration and neovascularization of HA-VEGF-incorporated bladder acellular constructs in mouse and porcine animal models. J Biomed Mater Res A 94(4):1205–1215. https://doi.org/10.1002/jbm.a.32777
53. Horst M, Madduri S, Gobet R, Sulser T, Milleret V, Hall H, Atala A, Eberli D (2013) Engineering functional bladder tissues. J Tissue Eng Regen Med 7(7):515–522. https://doi.org/10.1002/term.547
54. Oerlemans AJ, Feitz WF, van Leeuwen E, Dekkers WJ (2013) Regenerative urology clinical trials: an ethical assessment of road blocks and solutions. Tissue Eng Part B Rev 19(1):41–47. https://doi.org/10.1089/ten.TEB.2012.0136

55. Ling Q, Wang T, Yu X, Wang SG, Ye ZQ, Liu JH, Yang SW, Zhu XB, Yu J (2017) UC-VEGF-SMC three dimensional (3d) nano scaffolds exhibits good repair function in bladder damage. J Biomed Nanotechnol 13(3):313–323
56. Bishop ES, Mostafa S, Pakvasa M, Luu HH, Lee MJ, Wolf JM, Ameer GA, He TC, Reid RR (2017) 3-D bioprinting technologies in tissue engineering and regenerative medicine: current and future trends. Genes Dis 4(4):185–195. https://doi.org/10.1016/j.gendis.2017.10.002
57. Pi Q, Maharjan S, Yan X, Liu X, Singh B, van Genderen AM, Robledo-Padilla F, Parra-Saldivar R, Hu N, Jia W, Xu C, Kang J, Hassan S, Cheng H, Hou X, Khademhosseini A, Zhang YS (2018) Digitally tunable microfluidic bioprinting of multilayered cannular tissues. Adv Mater 30(43):e1706913. https://doi.org/10.1002/adma.201706913
58. Alarçin E, Guan X, Kashaf SS, Elbaradie K, Yang H, Jang HL, Khademhosseini A (2016) Recreating composition, structure, functionalities of tissues at nanoscale for regenerative medicine. Regen Med 11(8):849–858
59. Yudintceva NM, Nashchekina YA, Blinova MI, Orlova NV, Muraviov AN, Vinogradova TI, Sheykhov MG, Shapkova EY, Emeljannikov DV, Yablonskii PK, Samusenko IA, Mikhrina AL, Pakhomov AV, Shevtsov MA (2016) Experimental bladder regeneration using a poly-l-lactide/silk fibroin scaffold seeded with nanoparticle-labeled allogenic bone marrow stromal cells. Int J Nanomed 11:4521–4533 **(eCollection 2016)**
60. Moe AA, Suryana M, Marcy G et al (2012) Microarray with micro- and nanotopographies enables identification of the optimal topography for directing the differentiation of primary murine neural progenitor cells. Small 8:3050–3061