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REVIEW

Bladder Replacement Therapy

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Abbreviation used: UAB, underactive bladder; OAB, overactive bladder; CIC, Clean intermittent catheterization; EAU, European Association of Urology; MIBC, muscle-invasive bladder cancer; LDDM, latissimus dorsi detrusor myoplasty; RADM, rectus abdominis detrusor myoplasty; SMA, shape memory alloy; TRH, thermo-responsive hydrogel; MRB, magnetic robot bladder; AC, augmentation cystoplasty; PGA, polyglycolic acid; SMC, smooth muscle cell; ECM, extracellular matrix; μ-ILEDs, microscale inorganic LEDs

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ABSTRACT

The bladder, as a vital organ of the urinary system, facilitates urine storage and micturition. The bladder can store urine under low pressure, sense volume changes, and coordinate with the urethral sphincter to ensure autonomous and efficient urination and bladder emptying. However, irreversible bladder damage may result from various conditions, such as nerve injuries, aging, or metabolic syndrome, compromising its normal physiological functions and necessitating various interventions for anatomical and functional bladder replacements. This review aimed to summarize advances on anatomical and functional bladder replacements.

Keywords: bladder, bladder dysfunction, bladder replacement, artificial bladder, tissue engineering

1. DISEASES RELATED TO BLADDER DYSFUNCTION

As a hollow muscular organ located at the base of the pelvis, the bladder constitutes a part of the lower urinary tract along with the ureters and urethra, performing complex physiological functions of urine collection, storage, and excretion [1]. However, a multitude of diseases can cause irreversible impairment to bladder function, thereby disrupting the natural efficacy of bladder storage and voiding that may require surgical intervention or even radical cystectomy. Bladder dysfunction may stem from a wide array of pathological factors. Neuropathies affecting neural regulation of the bladder (**Table 1**) and diseases impacting contraction/relaxation of the detrusor muscle can lead to bladder dysfunction [2]. Non-neurogenic factors include infectious and inflammatory bladder diseases, such as schistosomiasis, tuberculous cystitis, radiation cystitis, interstitial cystitis, in addition to some congenital bladder disorders.

Underactive bladder (UAB) and overactive bladder (OAB) are two prevalent forms of bladder dysfunction [3–5]. UAB is often characterized by a decline in the strength and/or duration of the detrusor muscle contractions, resulting in prolonged bladder emptying time or failure to complete bladder emptying [6]. As UAB progresses, it can lead to serious complications such as upper urinary tract hydronephrosis and renal failure, posing a serious threat to the life of patients [7]. Some epidemiological studies have reported the incidence rate of UABs stands somewhere from 10% to 23%, and this rate is expected to increase with the aging of the population [8,9]. Clean intermittent catheterization (CIC), administered 4–6 times a day, is the preferred treatment for this condition, according to the European Association of Urology (EAU) guidelines [2]. Nevertheless, nearly 39% of patients may develop complex urinary tract infections post CIC, leading to a lifelong reliance on suprapubic cystostomy for urine drainage [10]. OAB, however, is characteristic of an unusually high frequency and urgency of bladder contractions [11]. Research indicates that up to 12% of adults experience OAB-related symptoms. Current conservative treatments, including behavior therapy and antimuscarinic drugs and β-adrenergic drugs, have proven to be suboptimal. Additional treatment alternatives, such as sacral nerve modulation, percutaneous tibial nerve stimulation, and an intra-detrusor injection of botulinum toxin A, remain unsatisfactory in terms of clinical efficacy [12].

Radical cystectomy should be considered for certain bladder-related diseases, such as bladder cancer. With over 400,000 new cases reported each year, the incidence of bladder cancer ranks the ninth globally among malignant tumors [13]. Over 1.6 million people worldwide suffer from bladder cancer, with lifetime risks

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for men and women estimated to be at around 1.1% and 0.27%, respectively [14,15]. Roughly 25–30% of bladder cancers are classified as muscle-invasive bladder cancer (MIBC), and more than 45% of patients with non-invasive bladder cancer are at risk of progressing to MIBC following treatment. Radical cystectomy remains the optimal treatment for MIBC [16,17]. MIBC is not the only indication for radical cystectomy; some conditions, such as interstitial cystitis, radiation injury, stenosis, tuberculosis, and trauma, may also require similar interventions [18,19].

Bladder dysfunction-related diseases clearly represent a global public health concern. Current clinical treatments often fail to effectively address the challenges associated with urine storage and impaired contractile function of the bladder, nor do they include complete bladder replacement after radical cystectomy. Therefore, there is an urgent need for further investigation on and development of bladder replacement therapies.

Table 1. Diseases and injuries possibly affecting bladder neural regulation

Possible factors	Diseases and injuries
Central nervous system-related factors	Cerebrovascular accident, traumatic brain injury, brain tumor, normal-pressure hydrocephalus, cerebral palsy, basal ganglia lesions, multiple system atrophy, ataxia, multiple sclerosis, spinal cord injury, intervertebral disc disease, and spinal stenosis
Peripheral nervous system-related factors	Diabetes, alcoholism, drug abuse, and sacral nerve root lesions
Infectious diseases	HIV, Guillain-Barré syndrome, herpes zoster, syphilis, tuberculosis
Iatrogenic factors	Spinal surgery, radical pelvic surgery, regional spinal anesthesia
Others	Hinman syndrome, systemic lupus erythematosus, myasthenia gravis

2. CURRENT RESEARCH

Researchers have proposed and investigated various approaches for the bladder replacement therapy. Despite substantial variations in these investigations covering clinical needs, material structures, and methodologies, they all revolve around the same goal, namely, to restore vesical functions or even physically construct a bladder functionally equivalent to the original. Directed at various types of bladder function deficiencies, these studies can be categorized into treatments that substitute for bladder contraction and bladder storage, and those offering a complete bladder replacement.

2.1 Treatments of substitution for bladder contraction

The immediate cause of bladder contraction dysfunction (*e.g.*, UAB) that prevents patients from initiating urination is a decrease in the strength and/or duration of bladder contraction. Thus, one solution proposed by researchers involves assisting in bladder contraction by wrapping muscles around the bladder or attaching external driving devices to the bladder, thereby enhancing bladder contractility.

2.1.1 Application of latissimus dorsi and rectus abdominis muscles

Initially, researchers considered wrapping the bladder with innervated skeletal muscles to enhance detrusor muscle function, thereby facilitating autonomous bladder emptying. With long pedicles and wide muscles, the latissimus dorsi and rectus abdominis muscles have been high on the list as choices for the treatment option.

Initially, the feasibility of transplanting the latissimus dorsi muscle to the bladder for detrusor myoplasty was experimentally studied by using a canine model [20]. A study published in 1998 first reported the treatment of three patients with low bladder contraction activities by employing latissimus dorsi detrusor myoplasty (LDDM). Postoperative follow-up showed that these patients could urinate autonomously [21]. Forte *et al*. [22] analyzed previous study data to determine if LDDM was superior to CIC. They noted that LDDM took an average time of 9 hours and that most patients attained a complete recovery, with spontaneous urination restored and a post-urination residual volume of less than 100 mL. Nonetheless, 30% of the patients ultimately required CIC. Since no comparative studies had been made, they were unable to compare these two treatment methods in terms of long-term outcomes [22].

Agarwal *et al*. attempted to utilize the rectus abdominis muscle as a replacement for bladder detrusor function [23]. They selected five male patients with a history of injuries below the T12 (subcostal nerve) level for surgery. During the operation, a portion of the rectus abdominis muscle was dissected, with the lower intercostal nerves and the inferior epigastric artery conserved. Subsequently, rectus abdominis was wrapped around the bladder. Postoperatively, the patients received instructions on practicing using abdominal muscles to urinate. Urodynamic comparison before and 1, 3, 6 months after operation suggested that rectus abdominis detrusor myoplasty (RADM) could improve spontaneous urination in patients with bladder contraction disorders resulting from a spinal cord injury.

2.1.2 Assistive devices for bladder contraction

The attachment of an external device to assist in bladder contraction offers certain benefits. Apart from reducing the risk

of iatrogenic surgical injury, the adjustability of such devices also allows for the accommodation of specific needs of different patients. This approach has been evaluated by various researchers.

Assistive devices for bladder contraction based on shape memory alloys (SMAs)

SMAs are a group of metallic alloys that can return to their original shape even if deformation occurs at lower temperatures with heating. Due to the simplicity and reliability of SMAs, these devices have long been applied in the medical field to provide muscle contraction as a compensation for lost or impaired muscle function [24–26].

Kiguchi *et al*. initially proposed a bladder-voiding device based on an SMA [27] that could assist urination by directly applying pressure on the bladder with a biocompatible Ti-Ni SMA spring. The effectiveness of this system was validated on a bladder model, as evidenced by less than 50 mL of residual urine in the model of SMA-assisted urination. However, further animal experiments have not been conducted. Subsequently, Hassani *et al*. introduced a flexible three-dimensionally printed implantable device driven by using SMA actuators [28]. Upon validation of device safety and surgical procedures using a rubber balloon in a rat bladder model, the device was tested on anesthetized rats, achieving more than 8% voiding volume. Hassani *et al*. continued to improve the device [29,30] and, in their most recent study, integrated a soft and thin capacitive sensor with an SMA-based actuator to establish a high-performance closed-loop system. Experimental findings indicated that this system could help the bladder reach a voiding volume ranging from 71% to 100% [31].

Hydrogel-based devices

Hydrogel is a hydrophilic three-dimensional network of cross-linked polymers that resembles the natural extracellular matrix. This imparts excellent biocompatibility, low immunogenicity, and biosafety to hydrogel [32,33], rendering it a popular material in recent clinical application research. Through intensive selection of materials, hydrogels can expand or contract under varying external stimuli [34]. Based on this principle, Yang *et al*. developed a balloon-like actuator comprised of composite hydrogel, flexible electronic devices, and silk scaffolds [35]. This composite hydrogel, consisting of a non-reactive strong hydrogel, a thermo-responsive hydrogel (TRH), and silk scaffolds, was used to wrap the bladder. A flexible Joule heater made of thin copper conductive film coated with polydimethylsiloxane and polyimide polymers was integrated into the composite hydrogel to heat the TRH, enabling it to contract and drive bladder contraction. The temperature-pressure relationship of the TRH has been verified both theoretically and experimentally. Animal experiments have shown that, with temperature increasing, the device could exert sufficient pressure on the bladder to induce urination.

Magnetic soft robots

Flexible robots, a class of robots based on responsive soft materials, emerged in the past decade. Yang *et al*. effectively integrated magnetic control technology, soft robot technology, medical polymer materials, and implantation technology to develop an implantable magnetic robot bladder (MRB), on the basis of flexible soft robots [36]. The MRB, when driven by a magnetic field, can contract the bladder as needed, thus directly applying mechanical pressure onto the bladder to assist urination. The biocompatibility and effectiveness of the device have been validated in a UAB pig model. Through computed tomography imaging and urodynamic characterization, the MRB-assisted urination has been demonstrated. The results confirmed that assisted urination could achieve the desired effect, without urine reflux into the ureter during urination. Given the similarities between pig and human bladders in terms of shape, capacity, and urodynamics, this research offers new possibilities for subsequent clinical applications.

2.2 Treatments of substitution for bladder storage

Patients with bladder storage dysfunction often fail to maintain the average urine storage volume of 400–500 mL of healthy individuals. This failure can be ascribed to either poor bladder compliance or small bladder capacity, or it may result from an overactive bladder detrusor muscle, or a combination of both. Sacral nerve stimulation or augmentation cystoplasty (AC) may be considered for the treatments of such disorders.

2.2.1 AC

The basic AC procedure involves anastomosis of a segment of the gastrointestinal tract to the bladder to increase its capacity, reduce intravesical storage pressure, and maintain the normal urination pathway. According to EAU Neuro-Urology Guidelines, AC can be used for overactive or poorly compliant bladders, and is especially recommended for refractory neurogenic detrusor overactivity [2].

Materials for autologous tissue

Proposed over a century ago, the use of gastrointestinal tissue for AC remains the first choice even today. Different portions of the gastrointestinal tract, including the stomach, small intestine, and colon, have been utilized for anastomosis with the bladder [37,38]. However, each has its own unique drawbacks. The most frequently used intestinal segment is the ileum 25–40 cm away from the ileocecal valve. Mundy *et al*. first performed the surgical procedure for ileal cystoplasty [39]. However, when the ileal mesentery is short, or its resection is contraindicated due to small intestinal pathology, the sigmoid colon becomes the optimal choice for the procedure [40]. The advantages of the sigmoid colon, as a material for AC, include a thicker muscle wall, larger lumen, and abundant mesentery [41]. Its drawbacks include increased mucus production and possible autonomous contractions, potentially leading to uncontrollable bladder contractions and higher-end filling pressure [42,43]. Another option is the cecal segment. The cecum, usually in conjunction with the terminal ileum, is also used for ileocecocystoplasty. This procedure utilizes the ileocecal valve as an anti-reflux mechanism [44]. The gastric segment is employed for AC when the intestine is unavailable or its use is contraindicated. The advantages of the gastric segment involve

reduced mucus secretion, decreased electrolyte absorption, and lower infection risk due to gastric acid secretion. The significant drawback, however, is a high incidence of malignant bladder tumors, reaching up to 10.3% [45]. Approximately 25% of patients also experience hematuria-dysuria syndrome, suffering from symptoms such as bladder spasms, pain, gross hematuria, and dysuria without infection [46,47]. Other complications include bladder peptic ulcers, perforation, electrolyte disorders, hypergastrinemia, and complications secondary to reduced gastric volume such as early satiety syndrome and dumping syndrome [46]. The high rate of postoperative complications, particularly the high incidence of malignant tumors, is a key reason why urologists seldom recommend gastric cystoplasty.

Other tissues have also been used in research on AC. In 1917, Neuhof first reported the utilization of fascia to enhance a canine bladder [48]. Further attempts have been made to use the peritoneum, greater omentum, placenta, submucosa of the small intestine, dura mater, and skin. However, these efforts have been unsuccessful [49]. AC can also be performed without using materials from the gastrointestinal tract. Cartwright *et al*. first described a procedure for children with neurogenic bladders [50]. The procedure involves cutting the patient's detrusor muscle to form a low-pressure diverticulum, thereby increasing bladder capacity and compliance. Although this procedure avoids complications associated with conventional AC, long-term studies have indicated suboptimal patient prognoses. Postoperatively, patients frequently developed serious progressive hydronephrosis, persistent urinary incontinence, and incomplete emptying [51]. Consequently, this procedure is rarely done in clinical practice.

Overall, while AC can improve bladder capacity, compliance, and urinary incontinence, and stabilize renal function to some extent for most patients, it is still not seen as an ideal treatment alternative due to severe complications (such as chronic urinary tract infections, bladder and kidney stones, metabolic sequelae, intestinal problems, perforation, and malignant tumors) and a high rate of secondary surgery.

Biomaterials

The application of autologous tissues carries certain disadvantages. Therefore, with the advent of biomaterials, researchers have begun to turn to biomaterials.

Biomaterials fall into two major categories: (i) permanent or biostable polymers, and (ii) biodegradable polymer scaffolds used for tissue engineering [52]. The former includes gelatin sponge, Teflon, polyethylene sponge, resin-coated paper, polyamine film, collagen, and silicone, among others. However, complications such as urinary calculi, postoperative fibrosis, scar formation, recurrent urinary tract infections, and graft contracture are common owing to issues related to structural function or biocompatibility [53], which restrict the effective application of these biomaterials.

As a result, researchers have shifted their focus to the latter, *i.e.*, biodegradable polymer. Tissue engineering is an interdisciplinary area that finds its applications in the development of biological substitutes for the restoration, maintenance, or improvement of tissue function [54]. In urology, tissue engineering-related research has predominantly centered on re-building the bladder wall, ureters, and urethra to fulfill the clinical needs of lower urinary tract reconstruction [55–57]. Generally, tissue-engineered bladder patches must meet several criteria: (1) the replaced tissue must be completely regenerated with the urothelium and muscle layer to secure related physiological functions; (2) tissue reconstruction must be swift and efficient to prevent early urinary leakage or bladder rupture and other postoperative complications; and (3) they must be safe on long-term basis within the context of tumor risk [58].

Bladder-related tissue engineering generally involves providing a bioactive matrix *in vivo*, leveraging the regenerative ability of the surrounding cells from healthy tissue to increase bladder capacity. As a better strategy, it consists of acquisition and cultivation of relevant cell lines, and then seeding them onto scaffolds *in vitro* before transplanting them into the body [59]. The first clinical study of cell-seeding tissue engineering on humans was conducted by Atala *et al*., who used the hybrid scaffold derived from collagen and polyglycolic acid (PGA) [49]. The study recruited seven patients with high bladder pressure and poor compliance due to myelomeningocele. Through bladder biopsy, smooth muscle cells (SMCs) and urothelial cells were extracted from each patient, cultured, proliferated, then seeded onto a collagen-PGA composite material, and implanted into the patients approximately seven weeks later. They found that these patients had a good postoperative recovery without severe complications. This result suggests that tissue-engineered biomaterial patches have a good prospect of application in AC.

However, the ideal material for tissue engineering remains has yet to be found, and the number and varieties of the materials under investigation continue to grow. The earliest bladder tissue-engineered scaffold materials were based on decellularized local tissues, which could provide extracellular matrix (ECM) signals and other endogenous growth factors to accelerate regeneration. In this context, the small intestine submucosa and bladder acellular matrix have received considerable attention [60]. Similarly, multiple studies examined the use of natural macromolecular components derived from ECM as bladder scaffolds [61–64]. Additionally, numerous materials and their combinations thereof have been trialed to create s caffolds, including silk fibroin, polyhydroxyalkanoates, hydrogels, PGA, and other α-hydroxy acid polyesters and their copolymers, such as polylactic acid-glycolic acid copolymers [65–71]. Currently, due to their unique properties, hydrogels have emerged as a preferred natural biomaterial for tissue engineering and in regenerative medicine [69,72–74,32]. Xiao *et al*. developed a three-layer scaffold composed of alginic acid-based and gelatin-based covalently crosslinked hydrogels, encapsulating adipose-derived stem cells. A silk mesh was positioned on one side of the hydrogel to enhance mechanical properties, while an acellular bladder matrix graft was placed on the other side as a waterproof barrier [69]. Their findings indicated that this composite material exhibited

excellent cell compatibility and superior mechanical properties, and inhibited fibrosis formation.

2.2.2 Optogenetic stimulation

Current clinical guidelines recommend sacral neuromodulation as a treatment strategy for OAB. This therapeutic approach involves direct electrical stimulation of sacral nerves, inducing inhibitory reflexes to suppress involuntary bladder voiding [75]. However, this stimulation can provoke adverse events such as pain, inflammation, and sacral nerve damage [76]. Further studies have revealed that direct electrical stimulation, when delivered to large nerve bundles, lacks organ specificity. This lack of specificity might activate neurons controlling the colon and other pelvic structures, resulting in side-effects, such as defecation difficulties [77].

Mickle *et al*. proposed a wireless closed-loop optogenetic system for specific sacral nerve stimulation [78]. This bio-optoelectronic implant continuously monitors bladder function via a precise, flexible biophysical sensor, and employs microscale inorganic LEDs (μ-ILEDs) to activate and control inhibitory proteins for optogenetic neural regulation. Preliminary experiments using mice and rats involved direct injection of herpes simplex virus vectors carrying inhibitory opsins into the bladder wall. Under the control of μ-ILEDs, neuronal excitability can be reduced. In a similar manner, Jang *et al*. employed scalable optoelectronic composites to precisely monitor the bladder condition in real-time and stimulate the bladder using μ-LEDs as needed, thus inducing voiding [79]. The primary distinction between these studies lies in their use of different viral vectors and expressed proteins for bladder remodeling. Results from both studies suggested restoration of disordered bladder function of some degree, indicating their potential clinical utility.

2.3. Total bladder replacement therapy

Currently, patients who undergo radical cystectomy can use autografts --- primarily gastrointestinal tissues --- as a replacement for an entirely removed bladder. However, similar to AC, this treatment frequently results in complications. To overcome the limitations of conventional gastrointestinal transplantation, research has been conducted to identify superior replacement materials. These studies involved the exploration of biodegradable polymer scaffolds for bladder tissue engineering [80] and permanent or biostable polymers for allogeneic or prosthetic materials [81]. The former approach focuses on scaffold-mediated regenerative medicine, aiming to construct a new bladder. In contrast, the latter aims to develop biostable bladder prosthetics, aiming at the development of implantable allograft bladders that accommodate the requirements for low-pressure urine storage and autonomous urination.

2.3.1 Bladder substitution with gastrointestinal segments

Patients undergoing radical cystectomy can elect to use a section of their own gastrointestinal tract as an autograft to substitute for the bladder. Depending on the type of urinary diversion planned, the isolated gastrointestinal tract is eventually reconnected with the remaining ureters to function as a replacement bladder [82]. Comparable to AC, different sections, ranging from the stomach to the colon, have been used for bladder reconstruction [83,84]. In clinical applications, different sections of the gastrointestinal tract were associated with unique advantages and disadvantages [85,86]. Due to its relatively long length, high mesenteric content, and ease of movement, the ileum has emerged as the most commonly used intestinal segment by urologists [84,87].

However, the physiological function of the gastrointestinal mucosa is to absorb water, electrolytes, and other nutrients digested from food. This function contradicts the non-absorbent nature of the bladder cavity, leading to clinical complications postoperatively due to long-term exposure to urine. These complications include electrolyte imbalance, metabolic disorders, urolithiasis, chronic infection, vitamin deficiency, and even secondary malignant tumors [88]. This highlights the inevitable limitations of conventional gastrointestinal bladder substitution procedures.

2.3.2 Bladder replacement therapy with tissue engineering

Tissue-engineered scaffolds are often confined to two-dimensional patches [52,89], used as AC materials. This strategy integrates biomechanical stability and tissue regenerative capacity. However, the shape, the types of cells involved, and the physiological interactions of hollow organs (such as the bladder, stomach, or uterus) are more involved.

In studies concerning total bladder replacement based on tissue-engineered scaffolds, Baumert *et al*. evaluated the feasibility of using the omentum as a natural bioreactor, and found that seeding scaffolds could mature in the omentum prior to being implanted into the bladder *in situ* [90]. Hoogenkamp *et al*. then developed a simple one-step casting technique to produce seamless, large, hollow collagen-based scaffolds. This model mimics the shape of an intact bladder and incorporates anastomotic sites for the ureters and urethra [91]. Bouhout *et al*. attempted to create a collagen-based bladder prototype [92]. Despite the fact that matured epithelial tissue was observed on this bladder prototype within 15 days, and the presence of differentiated SMCs confirmed, the density of its SMCs was relatively low compared to the muscle density of an actual bladder, indicating that further improvements are needed.

In bladder prototypes created with tissue engineering, it was reportedly possible to observe partial or full regeneration of the mucosal layer and detrusor muscle. However, their morphology and function do not perfectly mimic the native bladder wall, which affects its impermeability and compliance. Moreover, these bladder prototypes often exhibit inadequate vascular differentiation. This lack of sufficient blood supply further results in poor neuronal network regeneration. Additionally, the degradation products of scaffolds in the body may cause complications, including contracture, calcification, and fibrosis of the implant, thus limiting their potential for clinical application [52]. In con-

clusion, so far, these tissue-engineered substitutes are not superior to natural tissues and are not ready for application in a clinical treatment setting. However, the cultivation of a new bladder using tissue engineering and regenerative medicine methods remains a promising field of research.

2.3.3 Fully artificial bladder

Some researchers have tried to develop fully alloplastic artificial bladder models. These models are generally categorized into two types, in terms of whether the volume of the reservoir changes [93]. The first type is a fixed-volume model, based on rigid-walled containers, which fills with urine without the need for additional mechanical or electronic components and relies on gravity to discharge urine. The second type, the variable-volume model, works like a natural bladder, expanding and contracting, to a certain degree, to ensure low-pressure storage. These models typically incorporate additional components to facilitate changes in pressure within the reservoir chamber for urine filling and emptying. Compared to the former, the latter has yielded significantly better results in terms of bladder pressure measurements [94].

Material properties and performance remain the primary research challenges with this approach. Apart from the basic requirement of biocompatibility, the environment in which the device is implanted poses additional demands on the material [52,93,95]. First, the material should be non-absorbent and water-tight, forming a leak-free barrier to prevent urine from seeping into the abdominal cavity. Second, the alloplastic material should be structurally stable and easy to handle for surgical manipulation and operation. Third, the saline environment of urine requires that the material remain inert and resistant to corrosion and degradation. As ions in urine precipitate and accumulate, the surface of the material will scale. Therefore, the material should be resistant to scaling, to a certain degree, and to subsequent bacterial colonization. Finally, alloplastic biomaterials need to maintain these characteristics over a long period without deterioration.

In 1960, Bogash *et al*. first proposed an artificial bladder model made of silicone [96]. Since then, over ten other models have been established, all utilizing silicone, and were demonstrably insufficient for effective clinical applications [93]. If a material cannot fulfill certain prerequisites, it is inevitable that complications such as postoperative infections, scaling, hydronephrosis, and anastomotic urinary leakage are likely to develop. To work out a fully artificial bladder, researchers in recent years have proposed multiple new materials and designs, and subjected them to rigorous experimentation. Sharma *et al*. developed an allograft from polydimethylsiloxane-modified polyurethane aimed at preventing scaling and combating infection [97]. Other researchers employed a porous mesh-like substance as an external synthetic reinforcement, which encourages infiltration of natural cells and blood vessels, ensuring a secure attachment of the device to autologous tissue and successfully anchoring the urinary reservoir to the retroperitoneal space [93]. Moreover, to better mimic the function of the detrusor muscle, Casagrande *et al*. proposed to use a hydraulic actuator, and evaluated the urination efficiency of different types and configurations of actuators in various positions (horizontal, 45° tilt, and vertical) through bench tests [98].

However, these reported improvements have yet to satisfy the theoretical requirements of a fully artificial bladder since they all have limitations. Therefore, there is still a long way to the permanent or long-term implantation of a fully artificial bladder since this treatment approach remain in the preclinical experimental phase.

3. SUMMARY

In summary, some progress has been made in the field of bladder replacement therapy. However, most technologies under investigation remain in the experimental stage. In fact, bladder replacement therapy remains in its infancy, with the current body of evidence being inconclusive and insufficient to suggest that new treatment alternatives can outperform conventional autografts. These bladder replacement therapies, while displaying some feasibility, have yet to satisfy the requirements for clinical application.

As with any new therapy, the suboptimal results of preclinical or clinical research do not imply that bladder replacement therapy is incapable of further refinement into a medically acceptable approach. The rapid advancements in tissue engineering and biomaterials, coupled with an increasingly urgent clinical demand for treating bladder dysfunction-related diseases in our aging society, continue to fuel the interest in bladder replacement therapy among researchers and urologists. Despite a multitude of challenges, the research outlook for bladder replacement therapy remains optimistic. With ongoing critical reflection on past achievements, these preliminary attempts are likely, with active and meticulous evaluation and refinement, to ultimately pave the way for the development of standardized, reproducible bladder replacement therapies.

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