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Regenerative Medicine in Bladder Reconstructive Surgery

Ramnath Subramaniam *

Department of Paediatric Urology, Leeds Teaching Hospitals NHS Trust, Leeds, UK

Article info

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Abstract

This article explores the options for bladder reconstructive surgery and the role of regenerative medicine and tissue engineering. The indications for bladder reconstructive surgery are explored to complement medical management, which remains the first line for bladder dysfunction. Different strategies for research in tissue engineering of the bladder are discussed.

Patient summary: Options for bladder reconstructive surgery are discussed, including regenerative medicine and tissue engineering.

* Department of Paediatric Urology, Leeds General Infirmary, Great George Street, Leeds LS1 3EX, UK. Tel. +44 113 3926228.
E-mail address: r.subramaniam@leeds.ac.uk.

1. Introduction

The bladder is a complex organ with specialised functions of storage and volitional voiding of urine mediated by spinal reflex mechanisms involving sympathetic and parasympathetic neural pathways, respectively [1–3].

Storage of urine delivered by the kidneys is combined with maintaining its electrolyte composition via passive permeability and active ion transport [4]. The urothelium separates the bladder muscle from the urine and has mechanosensory attributes, and thus responds via endocytosis and exocytosis to physical and chemical changes such as intravesical pressure and urinary electrolytes [5,6].

2. Bladder dysfunction and its consequences

The pattern of normal reflex voiding can be disturbed by bladder and/or sphincter dysfunction. Any structural, neurogenic, or functional abnormality of the bladder, structural or functional outflow obstruction, or abnormal uroflow dynamics, as in severe vesicoureteric reflux, can have significant consequences along the entire urinary tract [7–9]. Some of these anomalies, such as posterior urethral valves [10,11], myelodysplasia, sacral agenesis, spinal tumours, and exstrophy of the bladder, can have a chronic impact causing detrusor hypertrophy and fibrosis, change the bladder from a highly compliant, supple muscular organ to a stiff and noncontracting organ with poor compliance, endangering the upper urinary tract and resulting in renal impairment or failure. In such circumstances, management options might involve replacing diseased portions of the bladder [12,13].

The natural history of the urinary tract in neurogenic bladder sphincter dysfunction that is not satisfactorily managed is one of deterioration in the vast majority of cases within 3 yr [14].

Management of bladder dysfunction is aimed at protecting the upper tract while imparting continence, with medical options the mainstay towards these goals, including anticholinergics [15], clean intermittent catheterisation (CIC) [16–18], and Botox injections into the detrusor [19,20]. Urodynamics plays an important part in decision-making [21,22]. In individuals for whom catheterisation per urethra is not possible, surgical creation of a

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Table 1 – Pros and cons of each bowel segment in bladder augmentation

Bowel segment	Pros	Cons	Refs
Urothelium-based	No cancer risk No metabolic changes	Unpredictable outcome	[31–34]
Colon	Easy to harvest Minimal metabolic changes	Cancer risk	[39,40,42]
Ileum	Easy to harvest Long experience Low cancer risk	Mucus Metabolic factors Perforation?	[30,40,43,44]
Stomach	Metabolic factors	Acidity Cancer risk	[36,37,45]

catheterisable channel via the Mitrofanoff concept facilitates CIC [23–26].

Portions of the diseased bladder may have to be replaced when medical management is insufficient, as in end-stage bladder disease.

3. Bladder augmentation

Urothelial-based strategies for augmentation include ureterocystoplasty (UC) and detrusorotomy with or without a seromuscular colonic patch (autoaugmentation, AA). UC is only appropriate in selected clinical scenarios and is not an option in most circumstances [27–30]. AA needs to be performed early to be effective and concerns regarding failure with limited success have been reported in isolated series, so AA is not an universally accepted option [31–34].

Enterocystoplasty is the most widely accepted procedure for bladder augmentation, with the ileum being the favoured segment and the most compliant [35]. Gastrocystoplasty is a less popular option because of unfavourable side effects [36,37]. However, incorporation of bowel segments into the urinary tract has some undesired consequences, primarily because the gut is structurally and physiologically not suited for prolonged exposure to urine [38].

Gut produces mucous [39] and with it consequences [40] of bacteriuria, recurrent infections, stones, metabolic changes in the long term, and unknown cellular effects including malignancy [41]. Table 1 highlights the pros and cons for each type of bowel segment in bladder augmentation.

4. Regenerative medicine and the bladder

Regenerative medicine involves diverse areas of tissue engineering, stem cells, and cloning with the common goals of "replacing or regenerating human cells, tissues or organs, to restore or establish normal function" [42]. It offers the possibility to replace old and damaged cells with genetically compatible young and functional cells [43].

Tissue engineering is multidisciplinary and combines the principles of cell transplantation, materials science, and engineering to construct functional tissues and supplement or replace diseased and defective body parts [44,45].

Ideally, a neoengineered bladder must be able to mimic filling and voiding as in normal bladder function. However, this is extremely complex and appears to be very distant in prospect. Therefore, a compliant neobladder with a good functional barrier (realising low pressure storage) but drained via CIC (replacing voiding function) could be a realistic prospect in the coming years.

5. Urothelial tissue engineering

Native urothelium is a quiescent tissue for which the turnover of cells is extremely slow, with few cells if at all in cycle. However, in response to injury, the urothelium adopts a proliferative wound-healing phenotype with high regenerative capacity in attempting to re-establish an effective urinary barrier [46]. This characteristic of the urothelium has been exploited in regenerative medicine laboratories, where urothelium can be freely grown via passaging.

For tissue culture to be considered successful, the cultured urothelium must bear a similar footprint to its native equivalent, meaning it should look and act the same as native epithelium. Lewis [4] outlined these features, including high transepithelial resistance (TER) (native tissues have TER $>$20 000 ohms/cm^2); low permeability to water and urea; composition of three distinct cells with an asymmetric unit membrane (AUM); expression of markers of terminal differentiation such as UPK III at the apical surface; and the presence of tight junctions.

Proliferative normal porcine urothelium is considered to be "leaky" in that it is a monolayer with poorly differentiated phenotype, thus allowing passage of urine to the suburothelial zone. Cross et al [47] showed that manipulation of culture conditions, such as inclusion of bovine serum, can induce normal human urothelial cells to propagate in vitro and form a urothelium with barrier properties [47].

6. Bladder tissue engineering strategies

Most strategies involve the use of a scaffold or matrix to support the development of new tissues. Scaffolds can be natural or synthetic. Natural materials can be in their original form, such as amniotic membrane [48]; in a processed form, such as bladder acellular matrix [49,50]; or in elemental form, such as collagen [51]. Synthetic scaffolds are typically made of poly-glycolic acid (PGA) or poly-lactic glycolic acid (PLGA) as materials approved by the US Food and Drug Administration [45].