Quick note on tissue engineering-based surgical measures to treat patients with neurogenic bladder-due detrusor/sphincter dyssynergia

Contardo Alberti

L.D. of Surgical Semeiotics

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To treat the neurogenic bladder-due detrusor/urethral rhabdosphincter dyssynergia, early combined clean intermittent catheterization/pharmacotherapy (anticholinergic-, β3-adrenoceptor agonist drugs) management may be at times crowned with success of preserving an adequate bladder compliance and renal safe conditions. The persistence, instead, of elevated bladder filling pressure levels with high voiding pressure/uroflow values, together with aberrant urethral rhabdosphincter electromyographic findings, make necessary the resort to surgery strategies, among which – a part from rhabdosphincterotomy or alternatively intrasphincteric botulinum A toxin injection or urethral stent insertion – the bladder augmentation cystoplasty, with either reconfigured bowel- or gastric segment, is today the most efficacious surgical measure to increase the bladder urinary storage meanwhile lowering bladder filling pressure. Given the enterocistoplasty-dependent both potential systemic metabolic imbalances – such as hyperchloremic acidosis/hypokaliemia, hyperoxaluria, bone demineralization, chologenic diarrhoea/steatorrhoea, vit B12 deficiency – together with bowel prosthetic mucus overproduction-due recurrent stone formation, and, sometimes, malignant complications particularly at the intestinal-urinary tract suture line, tissue engineering techniques have been taken into consideration, more than twenty years ago, as alternative measure for bladder augmentation cystoplasty, until to reach successful clinical validation just in patients suffering from either congenital dysraphism- or acquired spinal cord injury-dependent neurogenic bladder. Nevertheless, also the tissue engineering-made augmentation cystoplasty, as well as that bowel-based one, unfortunately remains influenced by spinal cord neuropathy-due dysfunctional effects, hence the tissue engineering research could be today directed to suitably overcome such disadvantageous conditions.

KEY WORDS: Augmentation cystoplasty, Pediatric surgery, Tissue engineering scaffolds, Urology

Introduction

Among the various manifestations of the neurogenic bladder, the impairment of detrusor/external urethral sphincter (rhabdosphincter) synergic coordination – as, indeed, the sphincteric contraction simultaneously to micturition, just so-called detrusor-sphincter dyssynergia (DSD) – due to neurologic lesions at different levels between the pontine micturition centre and that sacral spinal cord one (Table I), acts as the most considerable pathophysiological disorder leading to bladder outlet functional obstruction with a dangerous increase in both filling and voiding bladder pressure, up to give rise to renal damage 1-3. In effect, bladder filling pressure high levels, compared with the normal ones less than 10-15 cm H₂O – particularly with elevated “leak point” pressure more than 40 cm H₂O – and, in addition, the increase in bladder voiding pressure (whose normal values are 50-80 cm
H₂O for men and 40-60 cm H₂O for women), lead to the vesicoureteral reflux onset and/or the urine pyeloureteral drainage lowering with decrease in glomerular filtration rate until renal failure, what's more when such conditions are worsened by recurrent urinary infection due pyelonephritis ¹.

Preventive and therapeutic medical measures

The early postnatal assessment of DSD (Table I) makes feasible the timely beginning of clean intermittent catheterization (CIC) treatment together with administration of either anticholinergics (muscarinic-3 receptor blockers, such as oxybutynin, tolterodine, solifenacin, trospium as well as propiverine, that's endowed with calcium-antagonist properties too) or β₃-adrenoceptor agonists, such as mirabegron, or even, for the neurogenic bladder refractory to drug therapy, the into detrusor botulinum A toxin injection ¹,²,³.

Such, early adopted in infancy, combined measures are at times crowned with significant benefits among which preservation of a suitable bladder compliance, prevention or ready suppression of vesicoureteral refluxes, so it proving to be paramount to foresee a long term kidney safe conditions, in comparison with the unreliability of neurogenic bladder management restricted to the only”wait and see” watchful observation ¹,²,⁶.

Intriguingly, it has been shown, by an experimental research in spinal cord injured rats, that the herpes simplex virus vector-based delivery of GAD (glutamic acid decarboxylase, changing the glutamate to γ-aminobutyric acid, GABA) gene to bladder afferent nervous pathway, can lead – by inhibitory effects on excitatory brain stem-spinal neurotransmitter glutamate – to lower the urethral rhabdosphincter resistance during bladder micturition contraction, what making foreseeable a possible innovative approach to treat the spinal damage due DSD ⁷. Moreover, the histone deacetylase epigenetic inhibitors trichostatin A and valproic acid prove to be effective, in vitro, to decrease the collagen overproduction from neurogenic bladder-derived smooth muscle cell culture, that's why such drugs could be used to prevent the bladder fibrosis in patient suffering from this disease ⁸.

Basic surgical management

Though the early combined CIC-pharmacotherapy may be long-term useful to prevent, in the DSD disease, the decrease in bladder compliance with following renal function damage, otherwise the persistence of high bladder filling pressure values with worsening disease, make necessary the resort to surgical measures ³.

A part from either the insertion of a urethral sphincteric stent or intrasphincteric botulinum A toxin injection or even resection of urethral rhabdosphincter, together with a possible anti-vesicoureteral reflux operation (ureterocystoplasty), the most common surgical measure consists in the bladder augmentation cystoplasty using either a reconfigured intestinal- or gastric segment to increase bladder compliance with following decrease in filling/emptying bladder pressure ³,⁹-¹². Quite out of the current use is, instead, the detrusor multiple myotomy-based bladder autoaugmentation as no fulfilling any good expectation.

<table>
<thead>
<tr>
<th>Table 1 - Neurogenic bladder-related DSD: essentials on aetiology and diagnostic assessment</th>
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<tr>
<td><strong>AETIOLOGY</strong></td>
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<tr>
<td>Congenital diseases</td>
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<td>– either open or occult dysraphism/myelodyplasia, due to folic acid deficiency in childbearing age women and related to folate metabolism-involved genes. Particularly, mutations of VANG1 gene seem to be a risk factor for neural tube defects (2).</td>
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<td>– sacral agenesis</td>
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<td>Acquired diseases</td>
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<td>– spinal cord injuries from sporting/motor vehicle/at work accidents or occurring iatrogenically after aortic-vascular or spine surgery; transverse myelitis, spinal tumors, multiple sclerosis.</td>
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<td><strong>DIAGNOSTIC ASSESSMENT</strong></td>
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<tr>
<td>– serum creatinine;</td>
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<td>– post-void residual volume;</td>
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<td>– renal and bladder ultrasonography;</td>
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<td>– urodynamics: bladder compliance (bladder volume/detrusor pressure ratio); bladder filling-voiding pressures; bladder pressure-uroflow profile; combined urodynamic tests-fluorescopic videoimaging;</td>
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<td>– rhabdosphincter electromyography(particularly, electromyographic-uroflow profile study);</td>
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<td>– motor unit potentials;</td>
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<td>– X-ray imaging: intravenous pyelography and, particularly, voiding cystourethrography (VCUG);</td>
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<td>– three-dimensional bladder-kidney holographic imaging (US, CT, RM);</td>
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<td>– radionuclide imaging; static renal scan, functional diuresis renogram, radionuclide VCUG.</td>
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Unlike that colonic/sigmoid one, the most commonly bowel segment used for the augmentation cystoplasty is the ileum, whose detubularization on the antimesenteric border with fashioned into either “U” or “W” shape, allows to achieve a low pressure compliant reservoir. Unfortunately, several systemic metabolic imbalances resulting from either the exposure of absorptive intestinal mucosa to urine – hyperchloremic acidos/s/hypokaliemia, bone demineralization because of bone calcium carbonate-phosphate dissolution due to excess of serum hydrogen ions – or the removal of ileal segment – chologenic diarrhoea/steatorrhoea, hyperoxaluria, vit. B12 deficiency, hypocalcemia/hypomagnesemia – lead to discredit, together with bowel prostatic reactive mucus overproduction-dependent recurrent stone formation besides the possible onset of malignant pathomorphosis entero-prosthetic complications, the resort to bowel for the bladder augmentation 13,14. In this regard, the gastric augmentation cystoplasty shows, instead, a lower onset of metabolic-electrolyte imbalance – a part from sometimes the metabolic alcalosis – and has the advantage of less mucus production 3,11,12.

Just to avoid such deleterious events and otherwise given that the use of intestinal segments in bladder reconstructive surgery results to be impracticable in some conditions – such as short gut syndrome, chronic inflammatory bowel disease, previous abdominal-pelvic irradiation – research, at the 90s of the last century, has been turned to apply the tissue engineering technology to bladder augmentation cystoplasty 15-17.

Outlines on tissue engineering technologies to build wall bladder tissue

Such technologies provide intriguing opportunities to create de novo a tissue endowed with both urothelium barrier/sensory transducer- and bladder smooth muscle cell contractility properties. Besides ECM (extra-cellular matrix) component materials (collagen, laminin, elastin, hyaluronic acid, alginate, chitosan) and acellular tissue matrices (ABS, acellular bladder submucosa; SIS, small intestinal submucosa), several biodegradable synthetic materials (from, at first, polyactic acid, PLA, or polyglycolic acid, PGA and PLA-co-PGA acid, PLGA, to, more recently, electrospinning-produced fibrous polyurethane/terephthalate) have been used as a tailored scaffold for either “unseeded” (cell free) or “seeded” (with autologous either differentiated- or stem cells) tissue engineering modalities. Unfortunately, unseeded tissue engineered bladder constructs show, in the course of time, a wall fibrosis-due shrinkage with inadequate compliance 18-22.

The use of different types of stem cells – from natural stem cells including embryonic-, fetal-, and adult stem cells to laboratory procedure-generated stem cells as by either somatic cell nuclear transfer-mediated therapeutic cloning or adult somatic cell genetic reprogramming – avails of their peculiar active properties as self-renewal and specific cell lineage differentiation under adequate microenvironmental conditions (growth factors, cytokines, etc), so to be an intriguing source of mature cells for various tissue engineering applications among which, specifically, the bladder augmentation cystoplasty 23-26.

Out of thoroughly synthesis-obtained biomaterials, the Bombyx mori (or even spider) silk fibroin, at times tested in animal models to either coat the surface of polyurethane scaffolds or create a bilayer silk fibroin/SIS constructs, has been also used as template for bladder tissue engineering, it showing good both structural and mechanic properties, such as biodegradability and plasticity 27,28.

Clinical validation of de novo tissue engineering-based bladder wall fabrication – by means of autologous mature urothelial/smooth muscle cells seeded onto a composite PGA-collagen made 3D scaffold – has been, at first, successfully achieved, thanks to Atala and his group, by implanting such construct, with omental drap, in patients needing augmentation cystoplasty as suffering from myelomeningocele-induced poorly compliant/high pressure neurogenic bladder 29,30. More recently, a tissue engineered augmentation cystoplasty, for treatment of neurogenic bladder, has been successfully obtained by using SIS as a scaffold to rebuild a functional bladder tissue 31. Significant research projects are more and more intended to develop tissue engineered bladder constructs that can allow, besides a suitable compliance, also a native-like contractile prosthetic tissue-mediated efficacious micturition. Keeping to recent literature reports, it seems, indeed, that BAM (bladder acellular matrix) might be used to obtain a cell-seeded graft with possible hope of fabricating “off the shelf” replacement materials for augmentation cystoplasty 31,32. Nevertheless, for patients with CIC-drug therapy refractory neurogenic bladder-dependent DSD, any augmentation cystoplasty measure – so, even that tissue engineered-based – remains conditioned, as it’s well-known 33, by spinal cord neuropathy dysfunctional effects. Hence it would be suitable, for these subjects, to prepare a tissue engineered neobladder-urethral rhadosphincter complex construct – “idea” more easily conceivable rather than feasible and otherwise questionable as far as the below-pointed out clinical implications – that proves to be free from spinal cord neuropathic effects. Such construct might be made up of neo-bladder wall provided with embedded tension biomicro-electro-sensors (correlatively to intra-neobladder pressure) with micro-loop antenna to send, beyond a properly-subjectively adjustable wall tension value threshold, modulated wireless e-m signals toward a neo-rhabdosphincteral receiver/converter micro-electro-device to promote, in turn, by a suitable rhabdosphincter-tone-contraction inhibitory e-m field generation, its relaxation simultaneously with the neobladder contraction. What should be quite reversible following the micturition-due intra-neobladder pressure drop below the arranged levels 34.
As it has been above mentioned, such tissue engineered complex structure may be, in my opinion, fairly questionable given its functional features like “autonomous neurogenic bladder”, that pathologically results from loss of both sensory and motor innervation. Nonetheless, by also endowing the neobladder construct component with a intramural micro-electro device open to voluntary activation through wireless e-m signals transmitted from a special outside personal electrostimulator, it could make possible a voluntary micturition.

Intriguingly, quite out of synthetic biomaterials, Bombyx mori (or even spider) silk fibroin-made scaffolds, functionalized with ECM-protein coatings, have been recently tested, in a animal model, as templates for urothelial/smooth muscle cell-seeded bladder tissue engineering, so-built augmentation cystoplasty showing both compliance- and filling pressure cystometry-assessed acceptable values.

Moreover, tissue engineering research is more and more properly intended to identify, among the dynamic reciprocity-related microenvironmental cell/scaffold interactions, possible dangerous conditions that may be due to synthetic polymer-based scaffold toxicity (phlogogenic-, carcinogenic, immunoreactive effects) and, on the other hand, to try out innovative more harmless technological modalities such as that to rebuild a reliable bladder by scaffold-less autologous smooth muscle cell sheet engineering.

Conclusive remarks

Though the bladder augmentation enterocystoplasty today remains the gold standard of surgical options for the treatment of neurogenic bladder, however the alternative tissue engineering-based approach to rebuild a functional bladder, has the advantage of avoiding the intestinal segment use-related complications. Recent advances in the field of tissue engineering technologies make more and more validable, indeed, their applications for the augmentation cystoplasty in patients with neurogenic bladder, with foreseeable developments regarding the fabrication of suitable devices to overcome the neurogenic bladder-dependent detrusor-rhabdosphincter dyssynergia. The nanotechnologies are quickly opening considerable chances in tissue engineering by allowing the control of neo-tissue growth and morphogenesis at nano-levels, the nano-structured “smart” synthetic polymer-based scaffold surfaces mimicking, indeed, the ECM microarchitectural conformation. Nevertheless, just as regards the still sheerly imaginative perspective of neobladder/rhabdosphincter tissue engineered complex, its feasibility is, at the moment, questionable, given its foreseeable difficulties to properly support a bladder-sphincter physiological synergetic coordination together with micturition proper device-mediated voluntary activation. It is firmly agreed on this point that to actually reach favourable purposes in the field of tissue engineering – both in the experimental and clinical transplantation surgery – it is necessary to closely keep to highly rational criteria, clearly proved in really interesting studies.

Particular bioreactors, as dynamic specific cell culture pivotal tools, can provide different biomaterial-based “seeded” scaffolds with bladder tissue mechanical-functional properties, such as elasticity and compliance towards various filling pressure values, so it allowing scaffold conformational adaptive changes under various individual conditions.

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lodisplasia, or acquired to cause trauma spinal. Tuttavia, pure l'assetto vesicale ottenuto con ricorso all'ingegneria tessutale – alla pari dell'entero-cistoplastica d'ampliamento – rimane funzionalmente condizionato dall'afferenza di aberranti segnali nervosi ad origine dalla lesione midollare-spinale, con persistenza, pertanto, della disinnegria vesico-sfinterica. Risulta, quindi, sempre più rilevante il proposito di superare tale situazione mediante dispositivi innovativi possibilmente realizzabili con ulteriori affinamenti dell'ingegneria tessutale.

References


Commento e Commentary

Prof. LUCIO MIANO
Ordinario di Urologia
Università “Sapienza” di Roma

Trattasi di una revisione storica, ben esposta in modo chiaro e completo, delle principali problematiche, soprattutto terapeutiche, correlate alla presenza di una vesica neurogena da dissinergia vescico-sfinterica. L’aspetto di maggiore attualità è quello relativo all’utilizzo di biomateriali sintetici per l’ampliamento vescicale quando esista indicazione a questo tipo di intervento. La proposta, anzi l’idea, presentata dall’Autore, di costruire una vesica cosiddetta “intelligente”, capace cioè di attivare meccanismi funzionali (rilasciamento, contrattura, compliance) appare assolutamente entusiasmante. Qualche piccolo segnale applicativo a livello sperimentale è già apparso nella letteratura internazionale, soprattutto utilizzando biomateriali funzionalmente ancora più simili al tessuto vescicale normale con possibilità di contenere bio-micro-elettrosensori attivabili dall’esterno. La strada è comunque lunga e difficile ma assolutamente entusiasmante appare la più indicata per trovare una soluzione terapeutica ottimale ad una patologia urologica (congenita ed acquisita) così invalidante in termini fisico e psicologico.

* * *

The paper is a clear and comprehensive historical review of the main therapeutical issue related to problems of neurogenic bladder affected by bladder-sphincter dyssynergia.

The more actual hope is about the possibility of using synthetic biomaterials for bladder augmentation when there is indication to this type of reparative procedure. The author’s proposal, or better his idea, to build a so-called “intelligent” bladder, that means be capable of activating functional mechanisms (relaxation, contracture, compliance), is absolutely exciting. Some small previous experimental applicative examples in this field has already appeared in the international literature, especially using biomaterials functionally more similar to normal bladder tissue, with possibility of containing bio-micro-elettrosensors driven from the outside.

It is a difficult and still long road to go through, but probably it appears to be the more desirable project for realising an appropriate and optimal therapeutic solution for a urologic pathology, that is so debilitating in terms of physical and psychological consequences, whether congenital or in acquired events.