Metabolic and histological complications in ileal urinary diversion
Challenges of tissue engineering technology to avoid them

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Abstract. – Patients with ileal continent urinary diversion may present some awkward challenges to internists which have a considerable role in their long-term management. The potential metabolic complications result from both unphysiological exposure of the ileum to urine and decrease in absorbitive bowell capacity. Moreover, a variety of histopathomorphosic changes have been reported in ileal segment because of chronic exposure to urine. The risk of malignancy, particularly at ureteroileal anastomosis, is well documented in several large series but the mechanisms of development tumor in intestinal segments used for urinary diversion remain uncertain. In order to avoid both metabolic and tumoral complications of ileal urinary diversion, research has been conducted into using tissues other than bowell for bladder augmentation or replacement. Tissue engineering technologies provide intriguing means for the development of tissue that can mimic the barrier properties of the urothelium together with functional aptitudes of the smooth muscle wall. Recent advances in biomaterial sciences pose significant challenges for tissue engineering.

Key Words: Ileal urinary diversion, Metabolism, Malignancy, Tissue engineering, Urology.

Introduction

In bladder reconstructive surgery, bowell tissue, despite associated pathomorphosic-malignant and systemic metabolic complications, remains so far the gold standard since no better alternative has been proved to be available. Nevertheless, over the last decade, many experimental studies in animal models have been done to develop new strategies for more proper reconstructive solutions. In this way, tissue engineering technology can provide a means to build a functional bladder tissue.

This article is intended to outline, first, the pathophysiologic pathway of histological and systemic metabolic complications related to use of ileum in bladder reconstruction, and, in the second place, the tissue engineering technologies to create bladder tissue.

Pathomorphosic and Malignant Complications

Although most commonly reported in patients with colonic urinary diversion, malignancies, particularly at the uretero-intestinal anastomosis, may also occur in patients with ileal diversion. Their incidence appears to be difficult to quantify exactly because of the long latency period between surgery and recognition of tumor formation (mean range approximately 20 years in benign underlying conditions and 7 years if diversion was made for pelvic malignancy) in comparison with poor life expectancy of elderly patients.

Clinical and laboratory experience of the histopathological changes seen in ileal segments, incorporated into the urinary tract, can explain, if not the carcinogenetic mechanisms, at least their sequential pathway from postsurgical inflammatory responses to malignant transformation. Biphasic pathomorphosic events have been pointed-out, from more than 30 years, in our own experimental model (enterocystoplasty in dogs), by means of light and scanning electron microscopy: (a) in an early inflammatory phase (no more than 1 year from the surgery), mucus hypersecretion together with inflammatory cell reaction in the lamina propria, both of them as a tissue response to chronic irritative exposure to
urine; (b) in a late regressive phase (more than 1 year after surgery), decreased villus-to-crypt ratio toward the mucosal flattening, making the graft mucosa to be like intestine in celiac disease, together with uneven arising of transitional epithelium from the ureters onto the juxtanastomotic ileal mucosa\(^{10}\). A lot of literature on the pathomorphosis of ileal urinary reservoirs in animal models reiterates our findings. Such morphological changes have speculative and clinical implications because they can affect the functional properties of graft mucosa and predispose to malignant transformation\(^{2,5,11-14}\).

As far as carcinogenesis is concerned, our findings suggest the hypothesis that the preternatural histotectonic connections between ureteral transitional epithelium and paranastomotic intestinal mucosa, might explain the prevailing appearance of malignant changes just at the uretero-intestinal suture-line or very close to it, because of the cytokinetic instability that results from the altered transduction of both chemical (adhesion molecules, growth factors, etc) and physical (e-m intercellular communication) inductive signals between extracellular matrix (ECM) and cell compartment (surface receptors, cytoskeleton, nuclear matrix) in dissimilar, preternaturally interfaced, tissues. In fact, the network of both intra- and extracellular signals – cell signaling – plays an important role in the maintenance of tissue architecture and integrity of epithelial cell layers. Any change in the basement membrane, such as its disruption, that just occurs in our findings, can lead, through analogous ECM-cytoskeleton-nuclear matrix interactions, to altered gene regulation of the epithelial cells\(^{15-17}\).

By histochemical studies, phenotypic changes in the mucin-secreting cells, with the shifting from sialo- to sulfomucins, have been shown in the diverted mucosa of ileum as well as in colonic metaplasia, and have been thought as potential premalignant\(^ {1,8-20}\). Moreover, as ultrastructural changes in ileal mucosa chronically exposed to urine, more desmosomes, together with shortening of the microvilli, have been found\(^ {12,14,21}\). Also the chronic inflammatory response of ileal mucosa to urine may be responsible for the risk of malignant transformation because inflammatory cells overexpress several growth factors that have tumor-promoting effects\(^ {5,22}\). In addition to inflammation, other factors of carcinogenesis are suture materials, stones and persistent urinary infection.

Besides the adenocarcinoma other tumors, in ileal urinary diversion, are signet ring carcinoma, polyloid adenoma, transitional cell carcinoma, lymphoma, sarcoma, carcinoid. Most of these malignancies arise at the uretero-intestinal anastomosis or very close to it and are very aggressive. Patients with these cancers have a poor prognosis and an higher mortality than those with primary intestinal tumors. Nevertheless, the incidence of malignancy in ileal urinary diversion is lower than that in colonic one. Intrinsic genetic, biochemical and immunological ileal properties, such as an efficient apoptotic machinery, elevated concentration of hydroxylase and abundance of cytotoxic intraepithelial lymphocytes, have some antineoplastic protective effects\(^ {5,23-27}\).

**Systemic Metabolic Complications**

The potential metabolic consequences of incorporation of an ileal segment in the urinary tract are a result of both the chronic preternatural exposure of intestinal mucosa to urine (A) and the removal of the ileal segment required for the reconstructive procedure (B)\(^ {1,23-28}\) (Table I).

As far as the first condition is concerned (A), several factors affect this: length and surface area of segment used, contact time of the urine with intestinal mucosa, urinary ionic concentration and pH, degree of renal function. With regard to absorbative surface, a completely detubularized spherical-shaped reservoir gives the largest volume for the smallest mucosal surface area\(^ {28,34}\).

Whereas, physiologically, through the intestine, hydrogen (H\(^+\)) is secreted in exchange for sodium (Na\(^+\)) – cationic exchange – and bicarbonate (HCO\(_3\)\(^-\)) in exchange for chloride (Cl\(^-\)) – anionic exchange –, in ileal urinary diversion, instead, main active transfer, in response to excess of ammonium (NH\(_4\)\(^+\)), H\(^+\), Cl\(^-\) in urinary medium, is absorption of these ions in parallel with secretion of HCO\(_3\)\(^-\) and Na\(^+\). In short, Na\(^+\) is secreted in exchange for H\(^+\) and HCO\(_3\)\(^-\) for Cl\(^-\), resulting in metabolic hyperchloremic acidosis\(^ {1,23,29,31}\). Bone mineralization (rickets in children, osteomalacia in adults) may be a long-term complication of uncorrected metabolic acidosis because of bone cation/hydrogen exchange, the dissolution of bone mineral (calcium carbonate and phosphate) buffering the excess hydrogen ions. Moreover, the acidosis may inhibit the conversion of 25-hydroxycholecalciferol to 1,25-di-hydroxycholecalciferol in the kidney, thus decreasing bone mineralization\(^ {19,23,31,35,36}\). However, the develop-
ment of hyperchloremic acidosis in ileal reservoir is lower than that in colonic one24,35-38.

Low serum potassium may result from chronic metabolic acidosis which causes intracellular potassium depletion and renal potassium wasting, but ileal segment has a greater ability to reabsorb potassium compared to colon segment, thereby attenuating the risk of hypokalemia28,31,36.

Because of osmotic gradient, ileal reservoir may lose water into the lumen, while, on the other hand, some drugs (methotrexate, antibiotics, phenytoin, etc) or their active metabolites can be reabsorbed with the increased toxicity towards the liver, that has a pivotal role in drug metabolism, and the kidney as excretory target organ23,29,31,36,39.

Progressive mucosal atrophy of ileal segment, together with loss of microvilli, results in decrease in its absorptive and secretive functions, thus acquiring more proper barrier characteristics9,23,31,36. Nevertheless, it appears to be likely that only a chronic ischemia of the ileal graft might induce a significant decrease in its absorptive properties as it otherwise occurs in mesenteric arterial insufficiency syndrome.

As far as ileal resection-related metabolic outcomes are concerned (B), particularly the removal of distal ileum can result in important abnormalities such as altered bile acids reabsorption, fat mal digestion, decreased fat-soluble vitamin (A, D, E, K) and cyanocobalamin absorption.

Table I. Main metabolic abnormalities in patients with ileal continent urinary diversion.

<table>
<thead>
<tr>
<th>A) As outcomes of ileal urine storage:</th>
<th>B) As outcomes of ileum resection:</th>
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<tbody>
<tr>
<td>• Hyperabsorption of H⁺, NH₄⁺, Cl⁻</td>
<td>• Decrease in reabsorption of bile acids</td>
</tr>
<tr>
<td>• Hypersecretion of HCO₃⁻ and Na⁺</td>
<td>Reduced bile acid levels in portal circulation (loss of negative feed-back)</td>
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<tr>
<td>Metabolic hyperchloremic acidosis</td>
<td>Increased load of bile acids into the colon</td>
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<tr>
<td>• Bone mineral (calcium carbonate and phosphate) dissolution to buffer excess H⁺ions</td>
<td>Fat mal digestion</td>
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<tr>
<td>Release and loss of bone calcium</td>
<td>Increased hepatic synthesis of bile acids</td>
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<tr>
<td>Hyperphosphatemia</td>
<td>Chologenic diarrhoea</td>
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<tr>
<td>Hyperphosphaturia</td>
<td>Binding of fatty acids with calcium and magnesium to form soaps (→ steatorrhoea)</td>
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<td>Phosphate stone formation</td>
<td>Gallstone formation</td>
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<tr>
<td>• Wasting of water into the ileal segment because of osmotic gradient</td>
<td>Decrease in calcium available to bind intestinal oxalate</td>
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<tr>
<td>• Reabsorption of some drugs or their active metabolites excreted in the urine (increased hepatic and renal toxicity)</td>
<td>Reduced calcium and magnesium absorption</td>
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<td></td>
<td>Hypocalcemia hypomagnesemia</td>
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<td>Hyperoxaluria and hyperoxaluria</td>
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<td></td>
<td>Oxalate urolithiasis</td>
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<tr>
<td></td>
<td>• Decrease in Vitamin B₁₂ absorption</td>
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Low serum potassium may result from chronic metabolic acidosis which causes intracellular potassium depletion and renal potassium wasting, but ileal segment has a greater ability to reabsorb potassium compared to colon segment, thereby attenuating the risk of hypokalemia28,31,36.
The decrease in the reabsorption of bile acids leads to a reduced concentration in portal circulation, thus promoting, by loss of negative feedback, a rise in their hepatic synthesis, with the risk of gallstone formation. On the other hand, the increased load of bile acids passed in the colon induces water wasting and salt secretion (chologenic diarrhoea). Fat maldigestion allows fatty acids to bind with calcium and magnesium to form soaps, thus resulting in steatorrhoea and in decreased amount of intestinal calcium available to bind with oxalate, thereby a rise in free oxalate in the colon and, in turn, its hyperabsorption with following hyperoxalemia and hyperoxaluria, hence the risk of oxalate urolithiasis.

Vitamin B₁₂ deficiency is also recognized as abnormality that may arise from the removal of the distal ileum. In physiological conditions, cyanocobalamin, just released from the food by digestive enzymes in the gastric acid medium, binds, in the duodenum, to intrinsic factor and such complex, in the terminal ileum, is able to bind, in turn, to intrinsic factor receptor thus allowing the absorption of the vitamin. Therefore, resection of the distal ileum may induce B₁₂-hypovitaminosis. By assessment of complete cobalamin profiles (serum vit. B₁₂, methylenon acid and homocysteine) in patients with ileal urinary diversion, a much higher incidence of tissue cobalamin decrease has been pointed out than by assessing the vitamin B₁₂ level alone.

Low serum calcium and magnesium may result from ileal resection as well as from renal tubular loss of these cations, due to acidosis. Renal functional impairment, secondary to several causes (uretero-ileal reflux or stenosis, high storage pressure in the reservoir, persistent infection, stone disease), increases the risk of metabolic imbalances and, therefore, the preservation of renal function for successful ileal urinary diversion is of paramount importance.

New Technologies in Bladder Reconstructive Surgery

In order to prevent such problematic outcomes and considering that the use of bowel, in bladder reconstructive surgery, must be avoided in several conditions (inflammatory bowel disease, short gut syndrome, abdominal and pelvic irradiation), research has been conducted into utilizing materials other than intestine for bladder augmentation or replacement.

Alloplastic materials, such as polytetrafluoroethylene, polyvinyl and polyester sponge, silicon rubber, polyurethane, have been experimented in urologic reconstructive surgery but have to be discarded because of material-related negative outcomes: crystal incrustation, bacterial adhesion, fibroblastic reaction and graft shrinkage.

On the contrary, tissue engineering technologies provide intriguing means for the development of a tissue that can mimic the barrier/sensory transducer properties of the urothelium and the functional aptitudes of the smooth muscle wall. Current tissue-engineering technology include both unseeded (cell free matrix) and seeded (cell matrix) strategies. In the unseeded technique, naturally-derived acellular materials (SIS, small intestinal submucosa; BAM, bladder acellular matrix; ADM, acellular dermal biomatrix; collagen sponge) are incorporated directly, in vivo, in the bladder to promote a natural process of wall regeneration (guided tissue regeneration), the proliferation of urothelial and smooth muscle cells into these materials arising from the surrounding native tissue. Unfortunately, at long-term (more than 1 year of follow-up), such unseeded augmented bladders show increased collagen deposition and resultant wall fibrosis with inadequate compliance. In the seeded technique, instead, tissue-engineered bladder is built in vitro, by harvesting autologous cells from surgical material or biopsy samples obtained from the host urinary tissue, dissociating and expanding separately the urothelial and smooth muscle cells, then attaching them to synthetic biodegradable (poliglycolic- or polylactic acid; polylactic-coglycolic acid) or naturally-derived (SIS, BAM, collagen) three-dimensional matrix-scaffold, so as to be implanted into the native host. In animal model (subtotal cystectomy in dog with subsequent replacement with such engineered tissue), histological evidence showed a normal three-layered wall structure, consisting in urothelium, submucosa and smooth muscle, and both in vitro contractility studies and in vivo dynamic cystograms showed satisfactory functional outcomes. Moreover, smooth muscle cells engineered from cells of both normal and unhealthy animal bladders, showed similar phenotypic and functional characteristics, suggesting that muscle cells from diseased bladders can be engineered into normal tissue.
Encouraged by the results in various animal models, Atala’s group engineered human autologous bladder tissue for patients with end-stage bladder disease requiring cystoplasty; the composite biomatrix-scaffold, made of collagen and polyglycolic acid, has been proved to be optimal for the engineering of functional bladder tissue and the omental wrapping had an important role in the success of such tissue engineered cystoplasty because of its rich blood supply.

Nevertheless, potential limitations of in vitro tissue engineering are related to complexity of isolating autologous urothelial and muscle cell lines and co-incubating them onto a delivery matrix-scaffold. Moreover, although the current techniques for tissue engineering depend upon a specimen of autologous cells from the unhealthy organ of the patient, samples from an extensively damaged organ may not yield enough sound cells. Therefore, an intriguing and promising chance of cell-based bladder engineering is the resort to stem cells, which are capable of self-renewal and differentiation into various cell lineages (Table II).

Recent advances in biomaterial science pose significant challenges for tissue engineering. New generation of biomaterials – smart biomaterials – combines the properties of natural and synthetic biodegradable materials; natural materials mimic the native cellular environment while synthetic polymers allow a better control of material characteristics.

On this regard, carbon nanotubes have the potential for providing the necessary structural strength for polymer/collagen tissue scaffolding and are able, on the one hand, to impart novel properties to the biomatrix such as electrical conductivity, that may aid in directing cell growth and in forming neural network, and, on the other hand, to act as a vehicle for drug, growth factor and genetic material delivery. Moreover, implantable carbon nanotube-based sensors onto the matrix could be used to provide continuous monitoring of the in vivo performance of engineered construct, by measuring its biological processes such as angiogenesis and apoptosis.

In conclusion, in bladder augmentation or replacement, current techniques using the ileum may be associated with systemic metabolic complications (hyperchloremic acidosis, bone disease, electrolyte and acid/base derangement, fat malabsorption, nutritional deficiency) and malignancies of the intestinal graft. To avoid such negative outcomes, various solutions have been proposed but did not pass the preliminary feasibility controls.

A polydisciplinary approach combining tissue culturing and biomaterial sciences appears to be a suitable road for the development of bladder engineered tissue.

Although dramatic advances have been done in the field of tissue engineering, the building of a whole neo-organ for patients in need remains still an ambitious challenge.
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