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# When the Bowel Becomes the Bladder: Changes in Metabolism After Urinary Diversion



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**Urinary diversion is performed on a regular basis in urological practice. Surgeons and general practitioners are not always aware of the metabolic effects of any type of diversion. From the patient's perspective, diarrhea is the most bothersome complaint after urinary diversion. Rarely, this is accompanied by other malabsorption syndromes. Hyperchloremic metabolic acidosis is the "baseline" metabolic state of diverted patients. Other electrolyte disturbances are infrequent. Partly due to the acidotic state, bone health is at risk in patients with urinary diversion. Many patients are also subject to urinary calculus formation, both at the upper and lower urinary tract. The kidney function has to be monitored prior to, and lifelong after, urinary diversion and screening for reversible causes of renal deterioration is an integral part of the follow up.**

## INTRODUCTION

In urological practice, several conditions can lead to untreatable problems of the lower urinary tract. High-risk non-muscle invasive bladder cancers, after failure of intravesical therapy or muscle invasive bladder cancer mandating cystectomy, comprise the majority of patients. Other reasons to perform cystectomy are neurogenic bladder disease, urinary incontinence and vesicovaginal fistulae (see Table 1). In our high volume tertiary referral center, about 1 in 6 cystectomies will be performed for non-oncological reasons.

Historically, initial urinary diversion was performed by formation of a fistulous tract between the ureters and the bowel. Such derivations used the anus as the

continence mechanism. The occurrence of ureteral strictures, stone formation, ascending infections with sepsis and peritonitis lead to an early, and high, mortality rate. At the clinical level, urinary incontinence was frequent. Both advances in surgical techniques and in medical therapy (antibiotics, fluid management) have resulted in long life expectancy after urinary diversion at present. This means that we will not only have to address evident and severe metabolic problems after urinary diversion, but that we also have to pay attention to more discrete changes in metabolism that can affect quality of life in the long run.

Urinary diversions can be divided into non-continent diversions, continent diversions and orthotopic neobladders. When a bowel segment is incorporated into the urinary tract, not only does the direct metabolic consequence need to be considered,

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but also the consequence of removing the segment from the gastrointestinal tract. The majority of urinary diversions are constructed from terminal ileum or ileocolonic segments of the intestine. The rationale to take these bowel segments are: good mobility with relatively long and anatomically constant vessels, the caecum rarely has diverticula, easy harvesting and re-anastomosis of these bowel segments, and finally, when creating continent diversion the appendix can be used as a conduit or the ileocaecal valve can be used as continence mechanism. There is no ‘proof’ however that these segments are superior to other bowel segments.

The nature and the grade of metabolic effects will be determined by the duration of contact between urine and bowel and by the segment and length of bowel used. Metabolic changes begin immediately after diversion. In the immediate postoperative phase however, urinary catheters and stents drain urine from the diversion and diminish the contact with the intestinal mucosa. At the time of catheter removal (around postoperative day 10) the metabolic changes occur fully. Many complications, however, will only become clear months or years after the surgical procedure. Therefore, long-term follow-up and prevention of complications is mandatory. Although diversions have been performed for decades, many aspects regarding follow up and prevention of metabolic changes remain under debate. This field of study is hampered by a plethora of confounding variables (such as concomitant chemotherapy, neurogenic diseases, congenital anomalies, etc.). Therefore, good clinical studies are lacking and most recommendations are based on expert opinion and low quality data.

In this review article we will describe the relevant short and long-term metabolic changes in urinary diversion using ileal and ileocolonic segments. We will suggest a scheme for clinical follow up, treatment of metabolic changes and prevention of complications (see table 2 and 3).

### Surgical Aspects

Non-continent ileocutaneostomy or Bricker diversion is the most frequently used type of diversion worldwide. This procedure was popularized by Eugene M. Bricker (1). In this procedure, 15 to 25 centimeters of preterminal ileum is harvested. Reasons for its popularity over other types of diversion are the relative ease and simplicity of the procedure. It gives predictable functional results. There is no risk for unexpected incontinence, for urinary retention or for catheterization problems. The use of a

**Table 1. Indications for Cystectomy**

- Non muscle invasive bladder cancer after failure of intravesical therapy
- Muscle invasive bladder cancer
- Neurogenic bladder disease caused by:
  - o Spinal cord injury
  - o Multiple sclerosis
  - o Meningomyelocele
- Bladder pain syndrome
- Radiation cystitis
- Urinary incontinence
- Vesicovaginal fistulae
- Failed reconstruction after congenital anomalies (such as extrophia vesicalis)

short bowel segment and the fact that the segment does not function as a reservoir, implicates less metabolic effects. Nevertheless, about 10% of patients with ileal conduits will have metabolic disturbances requiring therapy (2).

Several pouches to create continent diversions or orthotopic neobladders can be constructed by detubularizing (i.e. opening the bowel at the antimesenterial side in order to abolish functional bowel contractions) a certain length of ileum. The W-pouch or Hautmann pouch, the Stüder pouch, the N-pouch and the Kock pouch are some popular variants on this theme (3-7) (table 4). In contrast to the ileal conduit, 40-80 centimeters of preterminal ileum are used for these types of diversion. The ileal segment is detubularized in order to create a larger, low pressure reservoir. In this way reservoirs can be made with capacities that are similar to the native bladder. As a consequence, urine will have a long contact time with the intestinal segment, allowing extensive metabolic exchange. The

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Clinical Problem	Advise	Discourage	Intervention
<b>Diarrhea</b>	<ul style="list-style-type: none"> <li>• High fiber intake</li> <li>• High fluid intake</li> <li>• Cholestyramine</li> <li>• Loperamide</li> </ul>	<ul style="list-style-type: none"> <li>• High fat intake if bile salt deficient</li> </ul>	<ul style="list-style-type: none"> <li>• Quantify stool output</li> <li>• Check for infectious etiologies</li> </ul>
<b>Urolithiasis</b>	<ul style="list-style-type: none"> <li>• High fluid intake (achieve urine output of 2000 mL)</li> </ul>		<ul style="list-style-type: none"> <li>• Urine culture</li> <li>• Check for acidosis</li> <li>• Consider fat malabsorption</li> </ul>
<b>Metabolic Acidosis</b>	<ul style="list-style-type: none"> <li>• Sodium bicarbonate (1 to 2g t.i.d.)</li> <li>• Sodium citrate (1 to 3g t.i.d.)</li> <li>• Nicotinic acid (500 mg to 2g q.d)</li> <li>• Chlorpromazine (25 to 50 mg q.i.d.)</li> </ul>		<ul style="list-style-type: none"> <li>• Monitor potassium</li> <li>• Consider calcium supplements</li> </ul>
<b>Altered Sensorium/Coma</b>	<ul style="list-style-type: none"> <li>• Lactulose</li> <li>• Neomycin</li> <li>• Rifaximin</li> </ul>		<ul style="list-style-type: none"> <li>• Check for hyperammonemia</li> <li>• Check for infection with urease producing bacteria</li> <li>• Check for obstruction</li> </ul>
<b>Low Vitamin B12 Level</b>	<ul style="list-style-type: none"> <li>• Daily oral supplement</li> <li>• Monthly intramuscular or subcutaneous supplements</li> </ul>		
<b>Renal Function Impairment</b>	<ul style="list-style-type: none"> <li>• Strictly monitor blood pressure</li> <li>• Appropriate Diabetes mellitus control</li> </ul>	<ul style="list-style-type: none"> <li>• NSAIDs, toxic substances</li> </ul>	<ul style="list-style-type: none"> <li>• Perform renal ultrasound</li> <li>• Consider nuclear scans</li> </ul>
<b>Need for New Medical Treatment</b>			<ul style="list-style-type: none"> <li>• Consider possible reabsorption in the intestinal segment</li> </ul>

longer part of bowel used to create these diversions will also influence gastrointestinal absorption more extensively as compared to an ileal conduit.

For ileocolonic pouches, the terminal ileum, together with caecum, are detubularized to create a reservoir. One of the most popular examples of these techniques is the Mainz pouch (8, 9). Metabolic consequences of these pouches are in general comparable to ileal pouches, although some differences exist. One of the main differences is the incorporation of the ileocaecal valve in the urinary tract, which will increase the rate of diarrhea in diverted patients.

### **Bowel Dysfunction/Malabsorption**

Harvesting a part of preterminal ileum can result in diminished bile salt and fat absorption. The longer the segment needed to create a urinary diversion, the more likely clinically important malabsorption will occur. After food ingestion, bile salts are secreted into the duodenum. They emulsify fats and are almost completely reabsorbed in the preterminal ileum, entering the enterohepatic cycle. When large amounts of bile salts reach the colon, they act as mucosal irritants, directly causing diarrhea. When the absorbing part of ileum is resected, even removing a relatively small part can cause bile salt malabsorption. Fat malabsorption only occurs when larger portions of small intestine are resected resulting in steatorrhea. Resection of the ileocaecal valve can result in bacterial overgrowth of the ileum. This further reduces the absorptive capacity, resulting again in bile salt and fat malabsorption. Resection of larger parts of the colon can diminish absorptive capacity for the alkaline ileal content and can manifest in dehydration and metabolic acidosis. The above described bowel dysfunctions seem to be more prevalent in patients with underlying neurogenic disease. Diarrhea is clinically the most important element to diminish quality of life after urinary diversion (6). In general, nutritional deficiencies are rare since large portions of jejunum are not used for urinary diversions.

The treatment of persisting bothersome diarrhea after urinary diversion consists of increased dietary fiber intake (in general in fruits, vegetables, whole grain products), diminished fat intake and adding cholestyramine if necessary. The dose of cholestyramine has to be increased gradually from 4 g b.i.d. to 8 g b.i.d. and should be taken separately from other medication. Long term, high dose use of cholestyramine can induce deficiency of fat soluble vitamins. If these measures

prove to be insufficient, gastrointestinal motility inhibitors such as loperamide 4 mg q.d. to 16 mg q.d. can be added. It is best not to advise fluid restriction, since patients with urinary diversion are subject to dehydration (10).

### **Renal Function**

From the age of 40 onwards, glomerular filtration rate (GFR) of adults decreases progressively with approximately 1 mL/min/1,73m<sup>2</sup> from an initial normal value of 100 to 130 ml/min/1,73m<sup>2</sup>. After urinary diversion, several factors may amplify renal deterioration. Stenosis of uretero-intestinal anastomosis results in ureteric obstruction with gradual kidney damage. Also recurrent infections and urinary lithiasis will have a negative impact on renal function. In theory, the incorporation of a bowel segment into the urinary tract induces urinary metabolite absorption and thus a variable and immediate decline in renal function. The exact impact of urinary diversion as such on renal function is not known (11). It has been shown that GFR decreases 15-25% after urinary diversion with a follow up of 11 years (12).

In a clinical setting, it is important to screen for reversible causes of upper urinary tract deterioration in every patient and to treat these causes accordingly. It is equally important to know the level of renal function prior to urinary diversion, as this may have an impact on future decisions. Long-term monitoring of renal function, at least annually, is advisable. Serum creatinine is not a sensitive parameter of renal function. The use of renal ultrasound together with serum creatinine is to be considered a screening method of the upper urinary tract. When in doubt, or when a more precise idea of renal function is required, nuclear scans to determine the GFR or diuretic renograms should be performed, or 24h creatinine clearance should be determined. In patients with diminished renal function, baseline renal function should be determined prior to diversion.

### **Acid Base Abnormalities**

In the bowel lumen, sodium (Na<sup>+</sup>) is secreted in exchange for hydrogen (H<sup>+</sup>); bicarbonate (HCO<sub>3</sub><sup>-</sup>) in exchange for chloride (Cl<sup>-</sup>). Since urine generally has high concentrations of ammonia (NH<sub>3</sub>), ammonium (NH<sub>4</sub><sup>+</sup>), hydrogen and chloride, these substances are reabsorbed in bowel segments exposed to urine. Inevitably, the presence of ileal and/or colonic urinary

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diversions implies a chronic acid load. Whether this also results in important metabolic acidosis for the patient depends on the specific patient (comorbidities), the bowel segment used, and the duration of contact of the bowel segment with urine (13). A mild, subclinical hyperchloremic metabolic acidosis is encountered in all patients that undergo urinary diversion using ileal and/or colonic segments. Probably, up to 20% of these patients will have episodes of severe acidosis (14); reduced kidney function increases this problem. An ileal conduit uses much less bowel length and has a much shorter contact time with urine when compared to a neobladder or continent diversion. Therefore, the metabolic challenge to the patient is much smaller. Ten percent of patients with an ileal conduit have been reported to have a clinically important metabolic acidosis after a median follow up of 1 year (13). In severe cases, this can result in muscle weakness and bone demineralization. In prospective series, the rate of metabolic acidosis in continent diversion and orthotopic bladder replacement varies between 26 - 45%.

The definition of metabolic acidosis is not universal; a venous sample bicarbonate level of < 21 mmol/L is often used (11). It is important to take a venous blood sample in the follow up of patients with urinary diversion. We will start alkalinizing therapy in all patients that undergo continent urinary diversion or a neobladder on removal of the catheters in the immediate postoperative phase. Patients with an ileal conduit will not receive routine alkalinizing therapy. In the first year we will see our patients for follow up at 6 weeks and at 2-3 month intervals. Alkalinizing therapy is diminished

in accordance with serum bicarbonate levels and will be stopped in a large proportion of patients. Of course, it will be restarted when low serum bicarbonate levels are encountered, even in conduit patients.

Alkalinizing therapy with oral sodium bicarbonate (1 to 2 g t.i.d.) is our routine therapy in restoring normal acid-base balance, but flatulence may diminish tolerance for this therapy. Sodium citrate (1 to 3 g q.i.d.) is a valuable alternative, but has a bad taste. When sodium loads are to be avoided (fluid retention/pulmonary edema, hypertension) nicotinic acid (500 mg q.d. to 2 g q.d. extended release tablets) or chlorpromazine (25 to 50 mg q.i.d.) can diminish the need for alkalinizing agents, through inhibition of cyclic AMP mediated chloride ion transport (15, 16).

### Electrolyte Abnormalities

Patients with urinary diversion suffer from depleted body potassium loads due to intestinal loss (secretion) and renal wasting. In general, this hypokalemia will not have important clinical consequences. One has to realize, however, that when metabolic acidosis is treated, potassium is exchanged with the intracellular space in the body resulting in further potassium depletion. Clinically, this can become apparent by muscle weakness. Several case reports of patients presenting with general muscle weakness, mistaken for Guillain-Barré syndrome, after ureterosigmoidostomy are reported in the literature (17-19). Therefore, one should not forget to supplement potassium (potassium citrate 15 mEq (approximately 1.6 g b.i.d. to q.i.d.) when correcting acidosis in urinary diversion (20).

Chronic metabolic acidosis in patients with urinary

**Table 3. Suggested Follow Up Scheme of Patients with Urinary Diversion**

Parameter	Pre	6W	3M	6M	12M	18M	24M	Yearly
Bicarbonate	X	X	X	X	X	X	X	X
Ionogram	X	X	X	X	X	X	X	X
Creatinin	X	X	X	X	X	X	X	X
Vit B12							X	X
Kidney Ultrasound			X		X		X	X
Bone Densitometry	?				?		?	?



diversion is continuously buffered by bone carbonate. This results in continuous calcium release from bone. This excess of serum calcium is excreted by the kidneys, where the presence of acidosis and sulfate further inhibit calcium reabsorption (21). Clinically important hypocalcaemia is not frequent. More importantly, these metabolic changes will influence bone mineralization, as will be discussed further in the article. Calcium supplements (500 mg to 1 g q.d.) are the treatment of choice.

Hypomagnesaemia is a rare condition after urinary diversion. Nutritional depletion often plays an important role, with associated renal wasting since renal tubular magnesium reabsorption is influenced by the altered calcium and sulfate metabolism, as well as by the acidosis (21).

### Vitamin B12

Vitamin B12 from food is bound to intrinsic factor (secreted in the stomach) and this complex is absorbed in the terminal ileum. Loss of important portions of stomach, or the use of the terminal ileum in urinary diversion, can result in vitamin B12 deficiency.

Radiotherapy may further predispose patients to this kind of malabsorption (22). In the well-nourished patient body stores of vitamin B12 are sufficient for 3 to 5 years. Clinically, insidious but irreversible neurological deficits and megaloblastic macrocytic anemia will occur. In our institution, we routinely check serum vitamin B12 levels after urinary diversion on a yearly basis starting two years after diversion. When vitamin B12 deficiency is suspected, supplementation is started. Oral supplementation with high doses (1 to 2 g q.d.) might be as effective as parenteral (intramuscular or subcutaneous) administration (1 g monthly) (23).

### Calculus Formation

A hyperchloremic metabolic acidosis results in an increased renal calcium and hydrogen excretion and is often associated with hypocitraturia. The presence of fat malabsorption can induce hyperoxaluria. Both will induce calcium phosphate and/or calcium oxalate stone formation. The tendency for dehydration in diverted patients further increases susceptibility to stone formation. Chronic colonization/infection of the diversion, especially with urease producing bacteria,

**Table 4. Gastrointestinal Segments Used in Urinary Diversion**

Type of Urinary Diversion	Bowel Segments Used (ileal and ileocolonic segments are the most frequently used segments)					
	Stomach	Jejunum	Ileum	Ileo-colic Segment	Colon	Rectum
<b>Non-continent</b>		Jejunal conduit	Ileal conduit (Bricker)		Colonic conduit	
<b>Continent</b>						
Pouch	Gastric continent urinary reservoir			Mainz, Le Bag, Indiana		
Neobladder			Camey II, Hautmann, Kock, Stüder, N-pouch	Mainz, Le Bag, Indiana	Detubularized right colon, sigmoid neobladder	
Anal Continence					Uretero-sigmoidostomy, Mainz II	Modified rectal bladder

will result in struvite and/or carbonate apatite stones. As a result, the incidence of renal stone formation increases in patients with intestinal urinary diversion. After 20 years of follow up, up to 20% of patients with ileal conduits will have renal calculi (14). In routine follow up of diverted patients, timely ultrasound of the kidney has to be incorporated to detect stone formation.

In the bowel segment used in the diversion, calculus formation can occur, partly due to the above mentioned metabolic changes. In addition, the presence of foreign materials (such as sutures and staples) will act as a nidus. Intestinal mucus can also function as a nidus for calcifications as well as harbor chronic infection, resulting again in struvite stone formation. The presence of residual urine after catheterization or micturition is an important risk factor for calculus formation and infection. Pouch calculi are reported in about 10% of patients with continent diversion. Initial reports mentioned up to 25% of calculi in certain pouches. Probably exposed staples in these techniques were responsible for these very high rates (24-26). The number of calculi in orthotopic neobladders is generally lower, probably due to better emptying of these reservoirs.

### Bone Metabolism

In theory, a major effect of urinary diversion on bone metabolism is demineralization and is to be expected. The chronic metabolic hyperchloremic acidosis is buffered by bone minerals. Mobilization of calcium, carbonate and sodium results in demineralization. Secondly, acidosis impairs renal activation of vitamin D, which is necessary for normal bone mineralization. Acidosis also activates osteoclasts, resulting in bone resorption. Due to the use of bowel segments in urinary diversion, intestinal absorption of calcium and vitamin D can also be impaired. Parathormone does not seem to play a role in demineralization after urinary diversion. Severe bone demineralization leading to osteomalacia in adults, or rickets in children, is not seen in current series of patients with urinary diversion.

At the clinical level, asymptomatic adults with normal renal function do not seem to have major changes in bone mineral density (27). However, patients with diminished renal function are particularly at risk for bone demineralization, as well as women and children.

It is thus not clear to what extent patients should be screened (repeated bone densitometry) or prevention undertaken in groups at risk (such as women, children

and patients with impaired kidney function). At least, increased attention to the risk of osteoporosis should be paid in these patient groups. Asymptomatic adults with normal renal function probably do not need specific bone density monitoring (27).

Treatment of metabolic acidosis by oral sodium bicarbonate or other alkalizing agents and administration of vitamin C supplements (500 mg to 1g/24h) are able to avoid bone demineralization (28, 29). In severe cases, supplemental vitamin D and calcium may also be necessary.

### Hepatic Metabolism

Urinary diversion results in increased ammonia reabsorption from urine in the bowel segments. The normal liver can adapt easily to this increased load. A protein rich diet will further increase the ammonia load. The liver uses ammonia in the ornithine cycle to create urea, which is in turn secreted through the kidneys. Preexisting hepatic disease can hinder the clearance of ammonia, resulting in hyperammonemia. Infection with urea producing bacteria (*Proteus mirabilis*, *Klebsiella oxytoca*, etc.) further increases the ammonia load in an acute way. In addition, endotoxins significantly affect hepatic transport and metabolism (30). Certainly in the case of urinary obstruction, such an infection can lead to hyperammonemic encephalopathy and even to hepatic coma (31). This is the most frequent cause of altered sensorium in patients with urinary diversion. In the absence of obstruction or in patients with non-continent diversion such as an ileal conduit, the occurrence of these complications is extremely rare.

Treatment consists of drainage of the obstructed diversion along with antibiotics. The use of non-absorbable disaccharides (e.g. lactulose enemata) and oral neomycin can diminish the nitrogen load for the patient. Although protein restriction may be advised, there is debatable evidence for this (32).

### Abnormal Drug Kinetics

Every clinician that sees patients with urinary diversions has to be aware that drug kinetics may be altered after urinary diversion. Substances that are secreted in urine can be reabsorbed by the intestinal segments that are incorporated into the urinary tract. This might have consequences for both diagnostic and therapeutic purposes. The clinical significance of this process is difficult to summarize in general terms, since an

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important interindividual variability in ileal absorption is present (33).

### CONCLUSION

When a urinary diversion is carried out, every patient will undergo metabolic changes. Depending on the bowel segment used, the length of the bowel segment, the duration of contact with urine and pre-existing renal function, these metabolic consequences will be more or less pronounced. In an ileal conduit, the short bowel segment with limited urine contact keeps metabolic changes as minimal as possible. Even this group of patients will have episodes of severe acidosis and will have a risk for renal function deterioration. Continent urinary diversion (cutaneous or neobladders) will result in longer contact between urine and intestinal segments. These patients will initially require sodium bicarbonate supplementation. Life-long follow up of all patients with urinary diversion is mandatory. We suggest obtaining at least biochemistry (including creatinine, ionogram, vitamin B12) and kidney ultrasound on a yearly basis. It is unclear whether patients should be screened for bone health, but one should be aware of the increased risk in women, children and patients with impaired kidney function. ■

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