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TOPIC PAPER

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Renal function in the setting of urinary diversion

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Abstract Incorporating bowel into the urinary tract sets the stage for a potentially dangerous situation for the upper part of this tract. Obstruction, reflux and chronic bacteriuria may develop, all of which can all be detrimental. Most reports on renal function have used IVP and serum creatinine only, methods which are inadequate for proper assessment. Long-term follow-up of patients with ileal conduit diversion reveals a high incidence of morphological and/or functional damage to the kidneys. Refluxing techniques for implanting the ureters have usually been employed. In patients with continent cutaneous diversion or orthotopic bladder substitution, some recent publications have shown rather well preserved glomerular filtration rates. Traditionally, antirefluxing ureteric implantation has been used in these patients. There is presently a trend towards refluxing anastomosis in this setting, providing a low pressure pouch has been constructed. However, pressure can be high in such pouches and bacteriuria is common. The consequences for the fate of the upper urinary tract is unknown and caution should be exercised in recommending such techniques. There is clearly a need for prospective randomized controlled studies on the issue of refluxing versus antirefluxing anastomosis in continent urinary reconstruction. Patients with continent or non-continent diversion should have lifelong follow-up with regard to the upper urinary tract.

Keywords Kidney · Renal function · Urinary diversion · Neobladder · Conduit

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Introduction

A variety of operative procedures has been described for replacement of the bladder after cystectomy or in conditions with severe dysfunction. Segments of bowel, ileum or colon or a combination of both, are increasingly used to reconstruct the urinary tract. An important requirement after reconstruction of the lower urinary tract, such as urinary diversion or orthotopic bladder substitution, is that it should not jeopardize the integrity of the upper urinary tract. The development of partial or complete obstruction of urine flow, reflux of infected urine and the formation of renal stones are all factors that may adversely affect renal function.

With the basic experiments of Coffey in 1911, it became clear that the kidneys need protection in the settings of infection, reflux and high pressure in the lower urinary tract [7]. Protection of the kidneys is crucial and antireflux implantation by submucosal tunnel became the standard technique for most surgeons who performed ureterosigmoidostomies [13, 31]. With the worldwide use of the ileal conduit since the 1950s [5], the severe complications seen after ureterosigmoidostomy could be reduced. However, long-term follow-up studies of patients with ileal conduits have shown that renal morbidity leading to functional deterioration develops in a significant number of cases [33, 38]. The colonic conduit with antireflux ureteric implantation was introduced in an attempt to preserve renal function [53]. Initial studies showed less renal damage with such a technique [4, 45], however, this was not confirmed in later reports [10, 21].

Today, continent reconstruction, i.e. orthotopic bladder substitution and continent cutaneous diversion, is the first choice in many centres. Numerous techniques have been designed to achieve the goal of reflux protection, reflecting the lack of a single method superior to any of the others. With the introduction of the principles of detubularizing and reconfiguring the intestinal

segments, thus creating "low pressure reservoirs", the concept of obligatory reflux protection has been challenged [20, 37]. In fact, this issue is one of the hottest topics in urology today. Stable renal function after direct ureteric implantation into detubularized reservoirs was reported after short-term follow-up. The main argument of those who advocate that the incorporation of an antireflux mechanism is unnecessary is that the benefits of reflux prevention with antireflux technique are lost because of a higher risk of stricture formation and upper urinary tract obstruction. A convincing answer can only be derived from prospective, controlled, randomized studies of a large number of patients with long-term follow-up, but no such study is yet available. The present review attempts to provide an update on relevant experimental and clinical studies within this field.

Experimental models

A causative relationship between intrarenal reflux (IRR) and renal scarring has been proven [19], and the occurrence of IRR has been related to the morphology of the renal papilla [19, 39]. The theory proposes that IRR occurs at the papilla as soon as the pressure gradient between the calyx and the collecting tubules is reversed (>10–15 mmHg). A prerequisite for scar formation is the morphology of the renal papilla and the theory explains why scars never develop in some kidneys despite reflux. Renal scarring and reflux nephropathy refer to changes associated with chronic pyelonephritis. The pathological changes of chronic pyelonephritis are unspecific, e.g. different processes such as obstruction, reflux and ischemia lead to the same end result.

The need to incorporate an antireflux mechanism is supported by experimental findings, also in so called " low pressure" reservoirs/cystoplasties [24, 25, 46]. In a collaborative study between the Department of Urology, University of Lund, Sweden and the Urology and Nephrology Centre, Mansoura, Egypt, the authors tested the hypothesis that under low pressure in an ileal cystoplasty there would be minimal effects on the kidneys with refluxing anastomosis at long-term follow-up [25]. Subtotal cystectomy and cup ileocystoplasty were performed on 13 dogs. Different methods of reimplantation were used: nine renoureteral units were refluxing, six were non-refluxing and 11 served as controls. Refluxing ureteric implantation was commonly associated with bacteriuria in the upper urinary tract and pyelonephritis. Antireflux ureteric implantation was beneficial for renal preservation in this setting. The findings are in accordance with other animal models in the setting of "low pressure" reservoir/cystoplasty [24, 46]. These findings are certainly alarming, although studies in humans are clearly needed to confirm this in patients undergoing continent urinary reconstruction.

Clinical studies on renal function methodology

Most clinical reports published on renal function after urinary diversion are retrospective. A comparison between studies is therefore difficult due to differences in patient age, the underlying disorder, the use of radiotherapy, peri and postoperative routines and in the duration of follow-up. Type of suture material, and the use of stenting, and if so, for how long, are other factors that might be of importance. The functional status of the upper urinary tract prior to urinary diversion is most valuable information, but this is often lacking in clinical reports. Another problem relates to the methods of measuring renal function after urinary diversion. Many reports rely on serum creatinine and urography, but both are imprecise for the purpose.

Urography gives no quantifiable physiological information and thus little is learnt about any loss of nephrons. Excretion of contrast material gives a crude estimate of renal function, stones are located, and dilation, which is of questionable significance, is seen. The serum level of creatinine is often used to evaluate the excretory function of the nephrons. The tubular secretion of creatinine is stimulated with a slight glomerular filtration rate (GFR) decline, and thus GFR must be reduced by approximately 50% (around 50 ml/min) before serum creatinine starts to rise. The sensitivity of plasma creatinine for the detection of early renal impairment is therefore very low.

More accurate methods of estimating renal function take into account the excretion and the plasma level of a substance freely filtered through the glomeruli, thus measuring GFR. If used after urinary reconstruction with intestinal segments, the substance must not be absorbed by the intestinal mucosa. Iohexol, a non-ionic contrast agent, has been suggested as a reference method for GFR measurements due to its technical simplicity [6]. Radioisotopes are also well suited for the routine evaluation of renal function [40], and in many centers the estimation of GFR using ^{51}Cr-EDTA is standard. One study has shown that this substance is not, or is only negligibly, absorbed from intestinal segments in contact with urine [8]. If renal function is estimated using creatinine clearance, diuretic conditions must exist to minimize the reabsorption of creatinine by the intestinal mucosa [35]. Others use the newer 99mTc MAG3 for this purpose [11, 36]. With renography, information is obtained on the total and separate GFR, effective renal plasma flow, upper urinary tract dilation with obstruction (obstructive nephropathy) and upper urinary tract dilation without obstruction (obstructive uropathy). Valuable information can be gained on renal scarring using tomographic techniques.

Techniques of ureteric implantation

Decades of dogma have taught us that obstruction, reflux and bacteriuria are detrimental to renal function.

Nevertheless, for the implantation of ureters into an ileal conduit an open refluxing technique has most often been used, although antirefluxing techniques have been available, such as the Le Duc technique [32] and the split-cuff ureteric nipple [54]. For a colonic conduit, an antirefluxing submucous tunnel implantation has been favored. With the advent of continent reconstruction, new techniques for achieving non-refluxing units have become available. One example is the afferent ileal loop, as in the Studer pouch [51]. Here the ureters are implanted directly end-to-side, thus in a refluxing manner, to the proximal part of an intact tubular 20 cm long ileal segment which opens into the pouch. This afferent limb will prevent reflux during voiding. In the latest report, ureteric stenosis occurred in four out of 148 ureters [52].

Another antirefluxing mechanism is the afferent nipple valve, which is an integrated part of the Kock pouch. In addition to stone formation on staples, progressive fibrosis of the valve with obstruction of urine flow seems to occur with increasing length of follow-up [23]. Afferent nipple dysfunction with fibrosis, stone formation on staples and prolapse of the valve amounted to 10.4%, in addition to a 2.2% incidence of stricture of the ureterointestinal anastomosis, in the large series from UCSC [47]. The complexity in construction of the pouch has led to the method being more or less abandoned. In some centres, it has been replaced by the T-pouch [48], which cannot be claimed to be technically simpler, and with an antirefluxing mechanism adopted from the idea of Abol-Enein, i.e. the narrowing of an ileal segment by stapling which is then placed extramurally.

The serous-lined extramural tunnel, ''the Abol-Enein technique'', has moderate complexity and can also be used for dilated ureters [1]. A stricture rate of 3.8% for operated patients has been reported [2].

The Le Duc technique implies that the ureter is placed in a 3–4 cm long ileal mucosal trough and that the mucosal edges are sutured to the ureteric adventitia [32]. It can be used for implantation into ileum or colon. Stricture rates reported vary widely; from 5% to 15% of operated patients [17, 34, 43]. A modification of the technique was associated with stricture in four of 117 ureters implanted into ileal and colonic neobladder [42].

The split-cuff ureteric nipple was originally described for implantation into an ileal conduit. However, this rather simple technique has been used for implantation into ileal as well as colonic neobladders with a reported stricture rate of 3/98 ureters [41].

For submucosal tunnel implantation into colonic segments, the incidence of stricture formation varies; from 6% to as high as 29% of operated patients [27, 30, 49].

Why do strictures form? The cause is often obscure in the individual case. Factors such as urine leakage at the anastomosis, poor blood supply with ischemia to the distal ureter, radiation, infection, and inadequate incision of the bowel where the ureter enters may be causative factors. Careful dissection and handling of the ureter is mandatory; ''The ureter is unforgiving'' (D. Skinner). It is conceivable that a simple end-to-side anastomosis with less manipulation of the ureter would result in less risk of stricture. However, this assumption has not been proven. In general, most studies on ureterointestinal anastomosis and outcome are fraught with inadequacies and the level of evidence is low. Stricture rate is sometimes given as a percentage of patients operated, sometimes of ureters anastomosed. There is no consensus as to what constitutes a stricture, nor how it should be evaluated. It seems that the stricture rates given are usually based on the number of ureters reimplanted and/or non-functioning kidneys . But how do we evaluate the result if separate renal function decreases from 50% to 25%? There is clearly a need for consensus on this issue.

Renal function after conduit urinary diversion

Many reports have revealed a high incidence (13–41%) of renal deterioration associated with a refluxing ileal conduit as evaluated by serum creatinine and urography [33, 38]. In a study of the long-term results of colonic conduit, Elder and associates [10] reported a significant deterioration in renal function (urographic) in refluxing units compared to those with an antirefluxing anastomosis. Renal units subjected to obstruction were excluded. Madersbacher and associates recently found renal complications in 27% (35/131) of patients 8 years after ileal conduit diversion [33]. Symptomatic urinary tract infection (including pyelonephritis) occurred in 23% (30/131) of the patients. In another long-term study, Singh et al. [44] reported dilated upper tracts in 44% of the patients, without giving functional data. In the series by Iborra et al. [22], a modest figure of 14% of patients followed for at least 10 years were found to have a decrease in renal function.

In a prospective randomized study, Kristjansson et al. evaluated patients undergoing conduit diversion or continent reservoir diversion. Renal function was evaluated after a mean follow-up of 10 years [29]. Patients undergoing conduit urinary diversion were randomized as to the type of intestinal segment (ileum or colon) and the technique for ureterointestinal anastomosis (refluxing or antirefluxing). If a $>25\%$ fall in total GFR is defined as renal deterioration, this occurred in 34% of the patients after a conduit diversion (40% in colonic and 28% in ileal conduit) and in 28% of those with a continent reservoir. However , the fall in the mean separate GFR did not differ between refluxing and antireflux ureteric implantation in the conduit group. The authors further investigated renal scarring and bacteriuria in the upper urinary tract in patients with conduit urinary diversion [26]. Severe renal scarring and bacteriuria in the upper urinary tract were more common on the side with a refluxing ureterointestinal anastomosis. The microorganisms were the same in the renal pelvis as in the conduits, suggesting ascending infections. These findings imply that antireflux ureterointestinal

anastomosis is important in preventing ascending infections and renal scarring in patients with conduit urinary diversion.

Renal function after continent urinary diversion

After continent reconstruction, renal function has most often been evaluated using serum creatinine and/or IVP only, and some reports do not give any information whatsoever, although "the urologist's main task is to preserve renal function" (H. Whitfield).

Few studies report on the GFR after continent cutaneous diversion or orthotopic substitution [11, 23, 29, 50]. In analyzing the figures, one has to take into consideration the known decline in kidney function that occurs with advancing age [15]. Thus, serial determination of ^{51}Cr-EDTA clearance in patients in these series indicates that GFR decreases somewhat with long-term follow-up. In general, however, renal function is well preserved. It compares favourably with that after conduit urinary diversion [29]. In young individuals followed for at least 10 years, 80% did not change renal function, while 20% had some deterioration, usually from identifiable and remediable causes [11]. Using urography to measure kidney morphology, stable renal function was reported with 7 years mean follow-up after construction of a Studer's ileal orthotopic substitution [52]. The ureterointestinal stricture rate in the series was very low (four of 148 units), with the ureters anastomosed to the proximal end of 15–20 cm of afferent tubular segment in an open end-to-side fashion. The authors suggested that the afferent limb in this technique protects the upper tract and incorporation of valves or other antireflux mechanisms is unnecessary. It was suggested that during the voiding phase Valsalva's maneuver increases the pressure simultaneously in the bladder, abdomen and renal pelvis and reflux does not occur. In addition, the urine was reported to be sterile in the ileal substitute.

The new trend

The presumption that non-refluxing ureteric implantation has a higher risk of stricture and upper urinary tract obstruction has lead some authors to abandon antirefluxing implantation techniques in continent urinary reconstruction using a "low pressure" detubularized reservoir [9, 16, 18, 20, 37]. Stricture rates reported in these series vary between 0 and 4.9% of implanted ureters. Using serum creatinine, IVP, renal ultrasound and contrast computerized tomography to evaluate renal function, the authors claim, after short to medium-term follow-up, that it is a safe option. These authors conclude "..we believe that antirefluxing ureterointestinal anastomosis in low pressure, high capacity reservoirs is unnecessary" (R. Hohenfellner et al. [20]), "We see no justification for any antireflux mechanism in neobladders" (R.E. Hautmann [16]) and "Reflux prevention in neobladders is even less important than in a normal bladder" (R.E. Hautmann [16]). These views are certainly contradictory to others: "The importance of preventing reflux of urine from a bowel substitution urinary reservoir into the upper urinary tract is unchallenged" [55]. This view is also supported by a report on a rise in serum creatinine and pyelonephritis at follow-up after conversion from ileal conduit to continent cutaneous diversion [3].

It is somewhat astonishing to note how quickly and unanimously the urological community has adopted the concept of the "low pressure pouch". Apparently all detubularized pouches are supposed to have low intraluminal pressure. However, no definition exists for the upper limit of "low pressure" pouches. An alarming report comes from Gotoh and coworkers [14]. They reported intraluminal pressure of 80–115 cmH_20 at micturition in 44% of their patients with orthotopic bladder substitution. This finding strongly contradicts the generally held belief that such continent reconstructive procedures always provide pouches with low pressure. The development of stenosis/dysfunction at the urethral anastomosis may further aggravate an intraluminal pressure condition. In addition, the lower urinary tract of patients with ileal or colonic neobladder is generally not sterile, although this is often stated. Careful studies have shown that neobladders are heavily colonized with potentially uropathogenic bacteria [56, 57]. If a proper antireflux technique is not used, or if there is an insufficiency in the antireflux mechanism, the microorganisms might spread to the upper urinary tract even if the reservoir's filling pressure is low. Whether such conditions are harmful to renal function is a matter of concern and should stimulate interest in long-term follow-up studies evaluating renal function.

We find it suitable to end this review by quoting another authority in his editorial comment on a paper on refluxing anastomosis: "In conclusion, while the dogma regarding anti-refluxing anastomosis can and should be questioned, evidence from the current study is neither sufficient, nor convincing. The potential advantage of reflux prevention as long as it does not add a risk of obstruction must also be considered. Randomized prospective studies are needed to clarify this issue" [12]. Indeed, such a study is underway. Patients undergoing orthotopic bladder substitution are entered into a prospective trial in which one ureter is implanted with and the other without reflux protection (A.A. Shaaban, pers comm). The result of this study is eagerly awaited. Until then the use of refluxing ureteral anastomosis in continent urinary reconstruction has to be considered experimental.

How should diverted patients be followed?

The EAU Guidelines (EAU Guidelines on Bladder Cancer 2001) proposes that patients are followed-up using serum creatinine, plain films and ultrasonogra-

phy. Serum creatinine is a crude measure of renal function, an appreciable amount of which can be lost without any significant change in the creatinine level. Plain film detects only stone formation and the problem with ultrasonography is that it gives no information about obstruction, which can be present with normal sonography, and conversely. In addition, it is user dependent. We think that IVP should remain routine at follow-up. As tubular damage precedes glomerular damage from postrenal causes, estimation of $alpha_1$-microglobulin in urine can be a suitable marker for tubular dysfunction [28]. If elevated, studies on GFR should be performed.

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