Original Article

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The Relationship Between Histological Changes and Urodynamic Parameters in Patients Undergoing Orthotopic Ileal Neobladder Surgery: A Case-Control Study

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Abstract

Objective: The relationship between histological changes and urodynamic findings emerging in neobladders (NBs) in a long term was not previously investigated. This study aimed to investigate the relationship between histological changes and urodynamic findings in the NB.
Materials and Methods: Patients undergoing radical cystectomy and Studer NB were included in the study. Patients with follow-up times <48 months were assigned to group 1 (n = 5) and those with follow-up times >48 months in group 2 (n = 6). Metabolic, endoscopic, histologic, urodynamic, and continence parameters were evaluated after surgery.
Results: No metabolic disorders or pathology was observed in the endoscopy of any patients. Histological evaluation revealed a decreased chronic inflammation and villus length severity over the years, with increased goblet cell numbers and fibrosis rates. Maximum reservoir capacity, compliance, and voiding pressure values for groups 1 and 2 were 418±42.1 and 401.33±67.8 mL, 15.65±2.7 and 18.54±4.98 mL/cm H_2O, and 28.2±2.28 and 30.6±7.4 cm H_2O, respectively. Maximum reservoir capacity was higher in group 1 than in group 2, whereas compliance and voiding pressure were lower, without significant differences (p = 0.84, p = 0.64, and p = 0.97; respectively).
Conclusion: No effects were observed on urodynamıc parameters resulting from the development of long term histological changes in the NB. However, the NB appeared to adapt to its new function by gradually assuming a similar morphology to the urothelium, maintaining a sufficient capacity and compliance. Daytime continence was achieved at a rate of 90.9%, without metabolic pathology.
Keywords: Neobladder, urodynamic, continence, histology, endoscopy

Introduction

Radical cystectomy (RC) is the standard treatment for localized bladder cancer in most developed countries (1,2). RC and urinary diversion constitute two steps of the same surgical procedure. Creating a continent, orthotopic neobladder (NB) diversion by pouch anastomosis prepared from the gastrointestinal tissue to the urethra, is one commonly employed technique for urinary diversion (1). Studer et al. (3) reported that the detubularized ileal pouch is used as an orthotopic bladder in patients with a healthy urethra after cystectomy and that the applicability of orthotopic bladder substitutions significantly increased thereafter. Orthotopic bladder substitutions are currently the method of choice in patients scheduled for RC due to their long term reliability and safety (4,5).

Various changes occur in the mucosa, which consists of a single-layer prismatic epithelium, due to constant urine exposure by the orthotopic NB. The absorptive and secretory functions of the mucosa decrease and microvilli are lost and shorten as a result of these changes. The cellular dynamics of the ileal mucosa undergo alteration, providing NB expansion and contraction. Thus, the NB replaces the bladder and begins adapting to its new environment. Micturition is achieved through abdominal muscle contraction, intestinal peristalsis, and sphincter relaxation. Various urodynamic changes and different urinary characteristics occur in these patients. The urodynamic analysis provides objective data concerning several urine volume measurements, enterocystometric pressure functions, and lower urinary tract functions (6,7,8).

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Several previous studies have investigated metabolic, functional, urodynamic, and histological NB findings (3,6,7,8,9,10,11). However, the relationship between histological changes and urodynamic findings emerging in NBs in the long term was not previously investigated. Therefore, this study aimed to investigate the relationship between histological changes and urodynamic NB findings and to collectively evaluate metabolic, endoscopic, functional, urodynamic, and histological findings emerging in the long term.

Materials and Methods

Study Population

The study protocol was approved by the ethics committee of the Dışkapı Yıldırım Beyazıt Training and Research Hospital (no: 92/22). Patients who had undergone RC due to muscle-invasive urothelial carcinoma (pT2N0M0) in recent years and received Studer orthotopic NBs as urinary diversions were included in the study. Patients were given detailed information about the study, and informed consent was obtained from all participants. Male patients, without surgical complications during the operation that affects the NB, not receiving adjuvant therapy, without urethral or anastomotic stenosis, not undergoing clean intermittent catheterization, without diabetes, and was operated on at least 36 months previously, were enrolled. A total of 20 patients initially provided the consent of participation; however, it was completed with 11 patients (Figure 1). Patients were given no additional medications during the postoperative period. All medical procedures in the study were performed by a physician (B.Y.K.).

Surgical Methods

A standard open surgical approach was adopted during all operations, and standard techniques were applied for orthotopic NB reconstruction, which involved a 45-50 cm ileal segment isolation approximately 20-25 cm proximal to the ileocecal valve. A proximal 15 cm ileum segment was left as an afferent limb. Next, approximately 30-35 cm of the ileal segment was subjected to antimesenteric border detubularization. The adjacent detubularized limbs were next folded into a U shape. The ureters were then anastomosed to the proximal afferent limb using the Wallace technique (Figure 2).

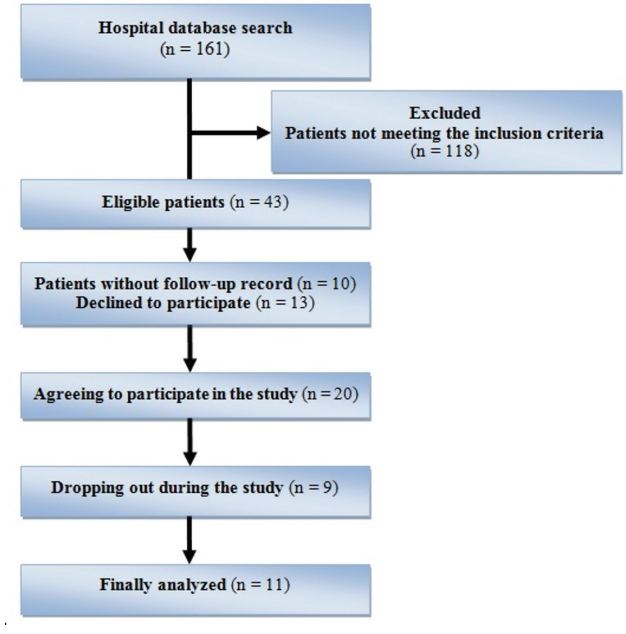

Figure 1. Flow chart showing the constitution of the study population

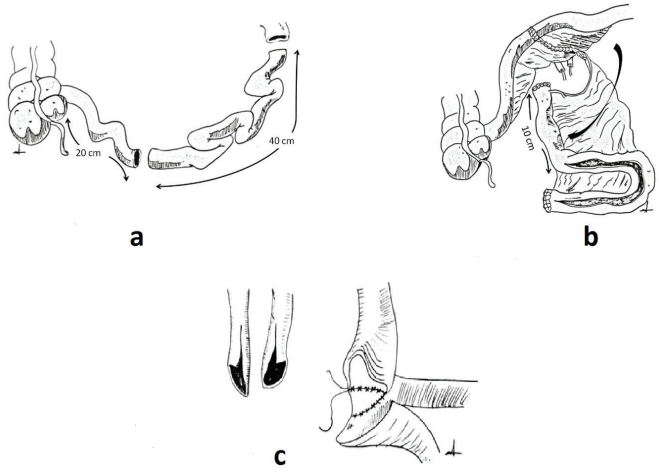

Figure 2. Surgical technique (a: Intestinal resection; b: Studer pouch preparation; c: ureteroilial anostomosis using the Wallace method)

Metabolic and Radiologic Evaluation

Hematological, serum biochemistry, and complete urine examination tests were carried out using commercial kits in line with the manufacturers' instructions. Arterial blood gas (ABG) was immediately studied on an autoanalyzer with specimens collected from the radial artery. The upper urinary tract was evaluated using renal ultrasonography.

Continence Assessment

Patients' daytime, night-time, and total continence were evaluated using standard assessment forms described by the International Continence Society (12).

Urodynamic Study and Evaluation of Voiding Function

Before the urodynamic study, patients were asked to void and postvoid residual volume (PVR) was evacuated by catheterization. Standard three-channel filling cystometry was performed using a 7 Fr transurethral catheter and 10 Fr rectal balloon catheters. Maximal cystometric capacity was determined through involuntary leakage or abdominal discomfort. In addition to maximal capacity, the first sensation of bladder filling, normal filling sensation, strong filling sensation, and compliance values were determined using cystometry (Figure 3). Uroflowmetry was performed after cystometry, after which PVR was measured using a fine catheter.

Endoscopic Evaluation

All endoscopic procedures were performed with the patient under general anesthesia. Mucous and accumulated debris were

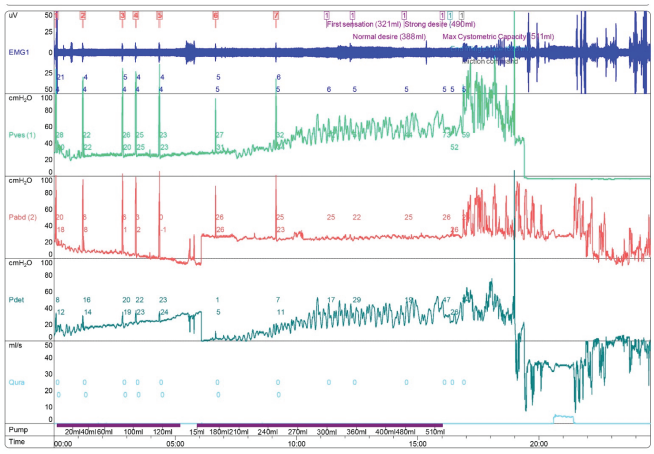

Figure 3. Urodynamic findings from one patient at 60 months postoperative

irrigated from the NB during the initial inspection as required. The pouch was first evaluated using systematic endoscopy, and multiple biopsy specimens were collected from four different regions: inferior, posterior, right, and left, using punch biopsy forceps.

Pathological Evaluation

Paraffin-embedded specimens were stained using hematoxylin & eosin (H&E) and periodic acid-Schiff (PAS). Villus length, crypt depth, inflammatory cell rates, muscularis mucosa thickness (MMT), dysplasia, and malignancy were evaluated on the H&E-stained slides, as previously described by Gatti et al. (8). Goblet cells were assessed with PAS staining. Villus length, crypt depth, and MMT on H&E-stained slides were determined numerically using an oculometer. The goblet cell ratio (GCR) was determined by calculating the proportion of positive cells to the total number of cells in the magnification field, as described by Gatti et al. (8).

The assessment of chronic inflammation defined moderate chronic inflammation as an intact mucosal epithelium, without erosion, preserved mucosal glandular structure and crypts, and inflammatory cells (lymphocytes and plasmocytes) infiltrating the mucosa. Severe chronic inflammation was defined as intensive chronic inflammatory cells causing mucosal surface epithelium erosion, eliminating the glandular structures and filling the mucosa. Samples were analyzed by the same unblinded pathologist.

Statistical Analysis

Data analysis was performed on Statistical Package for the Social Sciences 25 software (SPSS-IBM Corp., Armonk, NY, USA). The independent samples t-test was applied to determine the presence of significant differences in normally distributed continuous measurement variables between the two groups, and the Mann-Whitney U test for non-normally distributed continuous measurement variables.

Our study was conducted in compliance with the relevant directives and regulations (the Declaration of Helsinki and international good clinical practice guidelines). Detailed informed consent was obtained from all participants before procedures.

Results

Patient Characteristics

Eleven patients with a mean age of 62.63±6.63 years (range, 49-72) and mean follow-up duration of 48.54±13.54 months (range, 36-72) were included in the study. Patients were divided into two groups: 1) with follow-up durations of <48 months (group 1, n = 5) and 2) with >48 months (group 2, n = 6). Mean follow-up durations were 38.4±1.69 months (range, 36-45) for group 1 and 59±3.61 months (range, 48-72) for group 2. Patients had no previous urinary tract infections requiring hospitalization.

Metabolic and Radiologic Results

All patient urine cultures were sterile, but mucorrhea persisted in 10 patients (90.9%) at complete urine examination. Laboratory values were normal, without statistically significant difference between the groups. ABG pH values were 7.36±0.1 (range, 7.35-7.45) in group 1 and 7.37±0.1 in group 2 (p = 0.57) and bicarbonate values were 23±1 mEq/L (range, 22-26) in group 1 and 22.8±0.75 mEq/L in group 2 (p = 0.38). Mild hydronephrosis was observed in all patients in the renal ultrasonography but without kidney stones.

Endoscopic Results

The ureteral nipple was located in all patients in the endoscopic examination, with urine jet flow from the ureteral orifice. Pathological findings, such as stone, organized mucus, or anastomotic stricture, were not detected.

Urodynamic Parameters and Continence

The mean maximum reservoir capacity in the entire patient group was 409.09±131.98 mL (range, 138-561), mean compliance was 17.23±9.56 mL/cm H_2O (range, 2.15-32.85), and mean residual volume was 11.36±15.34 mL (range, 0-40).

The maximum reservoir capacity, compliance, voiding pressure, mean peak flow rates, and PVR for groups 1 and 2 were 418±42.1 mL vs 401.33±67.8 mL, 15.65±2.7 mL/cm H_2O vs 18.54±4.98 mL/cm H_2O, 28.2±2.28 cm H_2O vs 30.6±7.4 cm H_2O, 12.4±1.63 mL/s vs 16.3±2.18 mL/s, and 7±4.8 mL vs 15±7.52 mL, respectively. The group urodynamic and continence parameters are shown in Table 1.

No sensation of bladder filling occurred in any patients. Procedures were concluded due to abdominal pain in 9 patients and overflow incontinence in 2. The patients continued voiding by relaxing their pelvic muscles and continued with the Crede maneuver, which starts with abdominal straining.

Ten patients (90.9%) were daytime continent and eight (72.72%) were night-time incontinent. Two patients (18.18%) were fully continent and one (9.09%) was totally incontinent (Table 1).

No complications were observed in any patients during or after invasive procedures.

Histology

Light microscopy revealed significant histological changes. Severe chronic inflammation was observed in four patients in

Table 1. Comparison of urodynamic and continent parameters between the groups			
Urodynamic parameters (mean ± SD, min-max)	**Group 1 (n = 5)**	**Group 2 (n = 6)**	**p-value**
Max capacity (mL)	418±42.1 (283-537)	401.3±67.8 (138-561)	0.84
Compliance (mL/cm H_2O)	15.65±2.7 (8.3-24.4)	18.54±4.98 (2.1-32.8)	0.64
First desire (mL)	208.8±25.31 (131-287)	213±36.57 (50-321)	0.92
Normal desire (mL)	282±24.39 (213-336)	271.83±36.85 (119-388)	0.83
Strong desire (mL)	377.6±36.45 (273-494)	379.83±63.65 (129-526)	0.97
Pres first desire (cm H_2O)	15.8±4.6 (6-32)	11.16±1.57 (6-17)	0.33
Pres normal desire (cm H_2O)	20.2±3.44 (12-30)	21.16±4.85 (9-42)	0.88
Voiding pressure (cm H_2O)	28.2±2.28 (22-34)	30.16±7.4 (14-64)	0.97
Peak flow rate (mL/s)	12.4±1.63 (9-18)	16.3±2.18 (8-22)	0.2
Avarege flow rate (mL/s)	10±1.44 (6-13)	10±1.26 (6-13)	0.85
Voided volume (mL)	389±36.1 (286-505)	391.3±63.33 (143-550)	0.85
Residual volume (mL)	7±4.8 (0-25)	15±7.52 (0-40)	0.48
Day time continence			
Continent	5	5	0.81
Incontinent	-	1	
Night-time continence			
Continent	1	2	0.43
Incontinent	4	4	
Max: Maximum, Min: Minumum, Pres: Reservoir pressure, SD: Standard deviation			

group 1, and three in group 2 (p = 0.54). However, fibrosis was present in two patients in group 2, but in none in group 1. The mean villus length, crypt depth, MMT, and GCR values in groups 1 and 2 were 176±31.09 µm vs 140±41.06 µm, 196±25.41 µm vs 183.33±31.26 µm, 60±10.83 µm vs 34.16±11.43 µm, and 42±8.6 vs 55±10.56, respectively (Figure 4). No significant differences were observed in any histological values between the groups, and no neoplastic degeneration was determined in any patient.

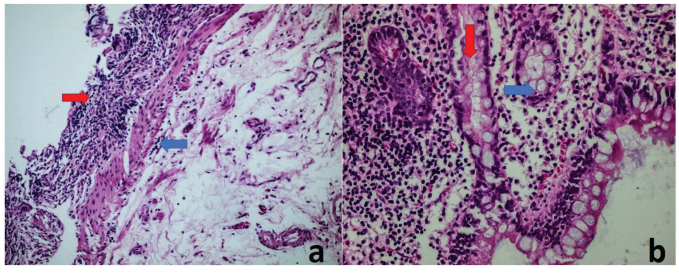

Figure 4. Histological evaluation of the neobladder; a, the muscular layer (blue arrow) and mucosa, but the mucosa is inflammatory (red arrow) and does not contain crypts and villi, H&E, x200 magnification; b, histological close-up view of the ileum mucosa: mucosal appearance with crypts (red arrow) and villi lined with numerous goblet cells (blue arrow), H&E, x400 magnification)

Discussion

This study investigated the histological NB changes and their effect on urodynamic parameters for several years (>36 months), which is the first in the literature to the best of our knowledge. The severity of chronic inflammation, villus length, and MMT in the NB histologically decreased over the years, whereas fibrosis and GCR increased. These histological changes were accompanied by increased urodynamic compliance, voiding pressure, peak flow rates, and residual volume, as well as decreased maximum capacity and first sensation volume. However, histological and urodynamic change differences between the groups were not statistically significant.

The current consensus is not available on the subject of NB urodynamic evaluation, and urodynamic parameters were similarly assessed in the intact bladder (13). The average maximum capacity of the ileal NB is 400-500 mL (13,14). The maximal reservoir capacities in the study groups in the present study were 418 and 401 mL, respectively. The compliance defined as the change in bladder pressure for a specific volume change is 5-10 mL/cm H_2O (14). NB compliance volumes postoperatively at 12-18 months in the literature range between 27.4 and 53.54 mL/cm H_2O (13,15). The mean compliance values in the present study were 15.65±2.7 in group 1 and 18.54±4.98 mL/cm H_2O in group 2. These low compliance values are due to the NB that achieves reservoir adaptation by undergoing histological changes due to the long follow-up period.

Daytime continence rates between 85% and 100% and night-time continence rates between 40% and 96.5% were reported in previous studies (14,16). Daytime continence rates in the present study were 100% in group 1 and 83.33% in group 2. The equivalent figures for night-time continence were 20% and 33.33%, respectively. Daytime continence was determined in 90.9% of the entire patient group and night-time continence in 27.28%. Our daytime continence rate was similar to that in the previous literature, but our night-time continence rate was lower. Due to the absence of afferent feedback and detrusor

sphincter reflex in the NB, urine begins to leak when the NB is filled as a result of nigh-time urine production (17). Age, physical condition, pelvic muscles, regular exercise, and excessive night-time urine production are all important factors in continence (14). The significance of these parameters in increased nocturnal incontinence rates is unavailable due to the limited number of patients with night-time incontinence.

Gatti et al. (8) reported villus length, crypt depth, MMT, and GCR basal values of 390 µm, 118 µm, 40 µm, and 16.1, respectively. Comparing these values in the present study, villus length significantly decreased in both groups, whereas marked increases were observed in crypt depth and GCR. Gatti et al.'s (8) study revealed villus length, crypt depth, and MMT values of 240 µm, 195 µm, and 52 µm, respectively in the fourth year postoperative. The comparable values in the present study for group 1 were 176 µm, 196 µm, and 60 µm, respectively. Except for the villus length, the morphological changes observed in this study were similar to those in Gatti et al. (8). These ileal histological changes lead to a decreased absorption capacity of the ileal epithelium and permit a functional reservoir the development.

Gatti et al. (8) reported that ileal adaptation occurs in two phases associated with chronic urine contact. In the first phase, aggressive injury occurs, such as shortening of the villi and increased crypt depth and MMT. In the second phase, these changes become permanent, with goblet cell predomination among the enterocytes. The rise in goblet cells increases over time. The first phase is concluded at the end of the first postoperative year, and then the second phase commences. Mucosal secretions change to sialomucins in association with increased goblet cells. This new secretion protects the mucosa against urine and allows the NB to adapt to the new environment. Gatti et al. (8) reported a basal GCR value of 16.1, rising to 32 at the end of 12 months and to 38 after 18 months. GCR values in the present study were 42±8.6 in the fourth year (group 1) and 55±10.56 in the fifth (group 2). GCR in the NB continues to increase in a time-dependent manner.

The mean MMT value in group 2, with a mean follow-up period of 59 months, was 34 µm. The equivalent value for group 1 was 60 µm. Gatti et al. (8) reported a basal MMT value of 40 µm, rising to 68 µm at the end of the fifth year, and decreasing over time to 52 µm in the fourth year. In the present study, fibrosis findings were present in group 2, but not in group 1. Although without statistical presentation, decreased MMT is related to fibrosis development in association with chronic inflammation in the muscularis mucosa. The urodynamic examination revealed the first desire, normal desire, and voiding reservoir pressures in groups 1 and 2 as 15.8±4.6 vs 11.16±1.57, 20.2±3.44 vs 21.16±4.85, and 28.2±2.28 vs 30.6±7.4 cm H_2O, respectively. A correlation was not found between MMT and urodynamic reservoir pressures in the present study.

Study Limitations

There are several limitations to this study. The most important is the limited number of patients. In addition, the patient's psychological state, regrets concerning surgery, and quality of life were not evaluated, which represents another major limitation. Despite these handicaps, this study is still valuable as the first of its kind in the literature. Further large, prospective investigation, and long term follow-up are necessary to confirm our findings and establish definite conclusions.

Conclusion

Long term histological NB changes do not affect urodynamic parameters. However, due to chronic urine exposure over the years, the NB adapts to the new environment by adopting a morphology resembling that of the urothelium. In the long term, sufficient capacity and compliance are maintained and daytime continence is established in 90.9% of patients, without metabolic pathology.

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Financial Disclosure: The authors declared that this study received no financial support.

Ethics

Ethics Committee Approval: The study protocol was approved by the ethics committee of the Dışkapı Yıldırım Beyazıt Training and Research Hospital (no: 92/22).

Informed Consent: Informed consent was obtained from all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Supervision: M.U.A., Critical Review: M.U.A., E.A., Concept: B.Y.K., F.Y., B.Ö., Design: B.Y.K., F.Y., Data Collection or Processing: B.Y.K., E.A., B.Ö., Analysis or Interpretation: E.A., F.Y., B.Ö., Literature Search: F.Y., Writing: B.Y.K., E.A., M.U.A., B.Ö.

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