Original Article

Increased detrusor collagen is associated with detrusor overactivity and decreased bladder compliance in men with benign prostatic obstruction

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ABSTRACT

Background: This study aimed to investigate the relationship between detrusor collagen content and urodynamic parameters in men with benign prostatic obstruction.

Material and methods: Nineteen consecutive patients undergoing open prostatectomy for bladder outlet obstruction (BOO) due to benign prostatic hyperplasia (BPH) were evaluated. Urodynamic tests were performed in all patients. BOO and detrusor contractility were assessed with the BOO index (BOOI) and the bladder contractility index (BCI), respectively. A bladder fragment was obtained during prostatectomy. Eight cadaveric organ donors composed the control group. Bladder sections were stained with picrosirius red and hematoxylin-eosin. The collagen to smooth muscle ratio (C/M) in the detrusor was measured and its relationship with urodynamic parameters was investigated.

Results: Seven (36.8%) patients were operated on due to lower urinary tract symptoms and 12 (63.2%) had urinary retention. The mean prostate volume was 128.6 cm^3 ± 32.3 cm^3, the mean BOOI was 76.4 ± 33.0, and the mean BCI was 116.1 ± 33.7. The mean C/M in BPH patients and controls were 0.43 ± 0.13 and 0.33 ± 0.09, respectively ($P = 0.042$). A negative correlation was shown between C/M and bladder compliance ($r = -0.488$, $P = 0.043$). The C/M was increased in BPH patients with detrusor overactivity (DO) compared to those without DO (0.490 ± 0.110 and 0.360 ± 0.130, respectively; $P = 0.030$) and also in patients with urinary retention ($P = 0.002$). No correlation was shown between C/M and maximum cystometric capacity, BOOI, or BCI.

Conclusion: Men with BOO/BPH have increased detrusor collagen content which is associated with decreased bladder compliance, detrusor overactivity, and urinary retention.

1. Introduction

Benign prostatic hyperplasia (BPH) is a common disease in aged men and is often associated with prostate enlargement and lower urinary tract symptoms (LUTS).[1] Bladder outlet obstruction (BOO) has long been considered a key factor in the mechanism through which BPH causes LUTS, and the relief of obstruction is the traditional basis of most therapies developed for the treatment of LUTS/BPH.[1] However, LUTS/BPH do not consistently correlate with parameters used for evaluating BOO, such as prostate volume, urinary flow, postvoid residual urine, and even pressure-flow parameters.[2] In addition, the mechanism through which storage phase symptoms develop in men with LUTS/BPH is unclear and many patients undergoing surgical treatment for LUTS/BPH persist with storage symptoms after relief of BOO.[3,4] In order to investigate the complex pathophysiology of LUTS/BPH, researchers have turned their attention to bladder abnormalities, and the findings support a major role for detrusor muscle abnormalities in the development of LUTS/BPH.[5]

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BOO induces morphophysiological changes in the bladder that may result in bladder dysfunction, including detrusor overactivity (DO), detrusor underactivity, and decreased compliance.[6,7] Men with BOO due to BPH (BOO/BPH) may develop detrusor hypertrophy and hyperplasia and accumulation of connective tissue within the muscle bundles.[8,9] On the one hand, detrusor abnormalities can be regarded as a consequence of BOO, but on the other hand, morphologic and functional abnormalities of the bladder can possibly have a direct role in determining LUTS/BPH.[5] Studies including men with BOO/BPH have shown increased collagen content in the detrusor.[9–11] It has also been suggested that the magnitude of detrusor collagen deposition is associated with the severity of LUTS in men with BOO/BPH.[10] Nevertheless, the interrelationship between detrusor collagen content and functional parameters, such as bladder capacity, DO, compliance, severity of obstruction, and detrusor contractility is poorly understood. In the present study we investigated the correlation between detrusor collagen content and urodynamic parameters in men with BOO/BPH.

2. Materials and methods

Over a period of 12 months, 19 patients (median age 69 years, range 62 to 81 years) undergoing open prostatectomy for BPH were enrolled in the study. Exclusion criteria were previous history of pelvic, bladder, or prostate surgery, previous pelvic radiotherapy, prostate or bladder cancer, presence of bladder stones, urethral stricture, and neurological diseases with possible impact on the lower urinary tract. This study was approved by the Institutional Review Board of the University of Sao Paulo School of Medicine, Brazil. Patients agreed to participate after full disclosure of its purposes and written consent was obtained from all participants.

All patients underwent a comprehensive evaluation including a focused urological history, international prostate symptom score (IPSS), physical examination including digital rectal examination, prostatic specific antigen level, urine analyses and culture, and transabdominal sonography for evaluation of the kidneys, bladder, prostate volume, and postvoid residual urine. All patients underwent urodynamics and definitions are in accordance with the International Continence Society terminology.[12] The urodynamic parameters evaluated were maximum cystometric capacity, bladder compliance, presence of DO, maximum flow rate during pressure-flow study, and detrusor pressure in the maximum flow rate. DO was defined as any involuntary detrusor contraction during the filling phase. Detrusor contractility was assessed with the bladder contractility index (BCI) and was considered normal if greater than 100.[13] BOO was assessed with the BOO index (BOOI) and was considered obstructed if BOOI was > 40 and unobstructed if BOOI was < 20.[13]

A full-thickness fragment of the bladder wall measuring 1.0 cm × 0.5 cm was obtained from the anterior bladder wall during prostatectomy. The specimen was fixed in 4% paraformaldehyde and embedded in paraffin.

The control group included eight cadaveric organ donors (median age 45.5 years, range 13 to 60 years), including five women and three men. No information regarding the history of LUTS and/or treatments for bladder or prostate conditions were available for the control group. At the end of the organ-harvesting surgery a bladder sample was obtained with the same technique used for BPH patients.

Bladder sections (4 μm) were stained with 0.2% sirius red–picric acid solution and hematoxylin.[14] A morphometric analysis of the muscle layer was performed, excluding the urothelium, lamina propria, and adventitia as well as blood vessels and nerves of the muscle layer. Collagen and muscle fiber quantification was performed with conventional point counting, using a 10× ocular lens containing a 49 point reticle.[10,15] Under light microscopy with 200× magnification, 20 noncoincident fields randomly selected in the muscle layer were analyzed. Polarized light was used to intensify the normal birefringence of collagenous fibers. The collagen to smooth muscle ratio (C/M) in the detrusor was obtained by dividing the sum of the collagen fiber area by the sum of the smooth muscle area of the examined fields.[9–11,16] We investigated the correlation between the C/M and urodynamic parameters.

Data were expressed as mean ± standard deviation or median and range. Results were compared using the Student t test or the Mann–Whitney test. The association between histological data and continuous variables was evaluated with the Pearson coefficient. A binary logistical regression model was used to evaluate the association between urinary retention and the C/M. Nominal variables were analyzed using the Fisher exact test. Statistical analyses were performed using SPSS 17.0 software (SPSS Inc., Chicago, IL, USA) and $P < 0.05$ was considered statistically significant.

3. Results

Seven (36.8%) patients were operated on due to LUTS refractory to medical therapy, and twelve (63.2%) had urinary retention requiring an indwelling urethral catheter. All patients with urinary retention had spontaneous retention and failed at least two attempts of catheter removal despite treatment with α-blockers for 4 weeks. Mean prostatic specific antigen level was 10.9 ng/mL ± 6.4 ng/mL (range, 1.6–27.4 ng/mL) and mean prostate volume was 128.6 cm^3 ± 32.3 cm^3 (range, 79.0–178.0 cm^3). Among the patients that did not have urinary retention, the mean IPSS was 24.9 ± 6.1 (range, 15–34). Urodynamic parameters of the BPH patients are shown in Table 1.

In controls the detrusor displayed organized muscle bundles with the connective tissue homogeneously distributed, surrounding individual muscle cells within the muscle bundles (Fig. 1A). In BPH patients the detrusor exhibited variable degrees of collagen deposition, heterogeneously distributed amongst muscle bundles (Figs. 1B, 1C). In many patients areas with massive collagen deposition were seen adjacent to normal smooth muscle fascicles (Fig. 1C). Mean C/M in BPH patients and controls were 0.43 ± 0.13 and 0.33 ± 0.09, respectively ($P = 0.042$).

A negative correlation was demonstrated between C/M and bladder compliance ($r = -0.488$, $P = 0.043$). No significant correlation was shown between C/M and maximum cystometric capacity, BOOI, and BCI. The C/M was increased in BPH patients with DO compared to those without DO (0.490 ± 0.110 and 0.360 ± 0.130, respectively; $P = 0.030$).

Table 2 compares BPH patients who underwent open prostatectomy due to urinary retention with those operated on due to

Table 1

Urodynamic parameters of men undergoing open prostatectomy due to benign prostatic hyperplasia.

|	Mean ± SD (range)
Filling cystometry	
Maximum cystometric capacity (mL)	330.0 ± 112.6 (160–500)
Compliance (mL/cmH$_2$O)	21.0 ± 15.1 (6.4–71.4)
Detrusor overactivity [a]	10 (53%)
Pressure-flow study	
Maximum flow rate (mL/s)	6.1 ± 4.0 (0–13)
Detrusor pressure during maximum flow rate (cmH$_2$O)	85.5 ± 30.7 (55–188)
Bladder outlet obstruction index	76.4 ± 33.0 (37–172)
Bladder contractility index	116.1 ± 33.7 (81–228)

[a] Percentage.
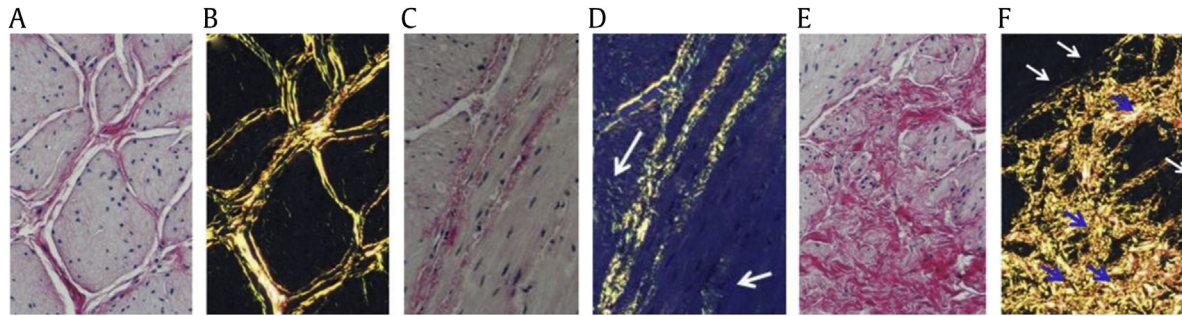
Fig. 1. Picrosirius red-stained sections of the bladder smooth muscle layer seen with and without polarization. (A, B) Homogeneous collagen distribution between smooth muscle cells and fascicles in an organ donor. (C, D) Mild collagen deposition (white arrows) throughout smooth muscle fascicles in a patient with benign prostatic hyperplasia. (E, F) Massive collagen deposition (blue arrows) next to normal appearing smooth muscle fascicles (white arrows) in another patient with benign prostatic hyperplasia. Magnification = 200×.

Table 2
Comparison of patients with urinary retention versus lower urinary tract symptoms refractory to medical therapy.

	Urinary retention ($n = 12$), mean $\pm$ SD	LUTS refractory to medical therapy ($n = 7$), mean $\pm$ SD	P
Age	70.0 $\pm$ 6.9	68.3 $\pm$ 3.9	0.558
Maximum cystometric capacity (mL)	296.4 $\pm$ 101.5	383.4 $\pm$ 104.5	0.079
Bladder compliance (mL/cmH$_2$O)	16.2 $\pm$ 9.6	29.2 $\pm$ 19.9	0.068
Detrusor overactivity [a]	67 %	14%	0.057
Bladder outlet obstruction index	84.9 $\pm$ 37.2	55.0 $\pm$ 11.5	0.029
Bladder contractility index	116.1 $\pm$ 40.1	116.0 $\pm$ 20.7	0.996
C/M	0.47 $\pm$ 0.11	0.35 $\pm$ 0.14	0.047

C/M, collagen to smooth muscle ratio; LUTS, lower urinary tract symptoms.
[a] Percentage.

refractory LUTS. The C/M was significantly higher in BPH patients undergoing open prostatectomy due to urinary retention. A regression logistic model demonstrated that the probability of urinary retention increases significantly as the C/M increases ($P = 0.002$) (Fig. 2).

4. Discussion

Experimental and clinical studies have demonstrated morphological, contractile, and biochemical changes in the bladder, which are associated with BOO.[5–7,17–19] Studies have consistently shown increased detrusor collagen content in animal models of

Fig. 2. Regression logistic model demonstrating the probability of urinary retention in patients with benign prostatic hyperplasia according to the collagen to smooth muscle ratio ($P = 0.002$).

obstruction as well as men with BOO/BPH.[6,7,9–11,16] The most often used method to evaluate the detrusor collagen content in men is the morphometric analysis of the muscle layer and calculation of the C/M. In the present study BPH patients had a C/M of 0.43, while it varied between 0.27 and 0.56 in other series.[9–11,16] For the controls the C/M was 0.33 in the present study and varied between 0.14 and 0.25 in other series.[9–11,16] These consistent results across the studies confirm that the morphometric analysis of the muscle layer is a reliable method to evaluate collagen deposition in the detrusor.

We have shown that the pattern of collagen deposition is heterogeneous, so normal detrusor may be found adjacent to areas with massive collagen deposition. Consistent with this finding, Brierly et al[20] used electron microscopy to show that the ultrastructural detrusor changes associated with BOO/BPH were localized and patchy. Such heterogeneous distribution may result from localized and restricted mechanism (e.g., hypoxia) in poorly vascularized muscle bundles and it is possible that the high voiding detrusor pressures associated with BOO/BPH may further potentiate cellular injury in this setting.[20]

Few studies have investigated the correlation between the detrusor collagen content and urodynamic parameters in patients with LUTS/BPH.[10,16] The interrelationship between collagen deposition in the detrusor and severity of BOO, DO, bladder compliance, and detrusor contractility remains unclear. In rats, surgically induced partial BOO initially leads to a decrease in the C/M due to an increased amount of muscle tissue.[21] As the bladder passes into a later decompensated state, increased collagen deposition is observed. These progressive pathological changes may also occur in men with LUTS/BPH.[21] This hypothesis is consistent with our finding of higher C/M in BPH patients with urinary retention compared with those with LUTS refractory to medical therapy. Urinary retention is one of the main signs of bladder decompensation. In our series, as the collagen content increased, so did the chance of urinary retention. Based on that finding we developed a logistic regression model, estimating the probability of urinary
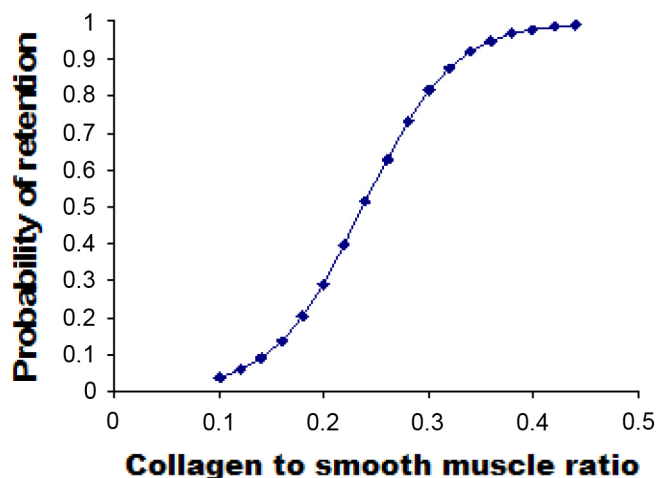
retention based on the C/M. Similar to our results, Collado et al[16] found increased collagen deposition in the detrusor of men with LUTS/BPH who had at least one episode of urinary retention. Increased collagen deposition could contribute to impaired detrusor contractility, as suggested by Elbadawi[22] using electron microscopy. In our series, however, detrusor contractility was not lower in patients with urinary retention. It must be acknowledged that our patient population was small and relatively homogenous in terms of severity of LUTS and BOO, which limits the ability to perform subgroup analysis or study the impact of differing degrees of urodynamically defined parameters of bladder function. Collado et al[16] showed a positive correlation between C/M and the severity of obstruction, but did not evaluate detrusor contractility. Further evaluation of a larger number of patients will be necessary to ascertain the association between collagen deposition and impaired detrusor contractility.

Decreased bladder compliance may be found in men with LUTS/BPH and is considered a sign of bladder decompensation.[23,24] Previous studies showed that increased detrusor collagen deposition may lead to a reduction of bladder compliance in BPH patients.[25,26] Our results are consistent with these studies, showing that collagen deposition increased as bladder compliance decreased; this supports the theory that the extracellular matrix components are the most important elements associated with the viscoelastic properties of the bladder wall.[27]

The association of detrusor collagen deposition and LUTS severity has also been explored. Mirone et al[10] found that among 36 men with BOO/BPH, the detrusor collagen content was higher in those with severe LUTS (IPSS 20—35) compared with those with moderate LUTS (IPSS 8—19). However, Collado et al[16] did not demonstrate a significant correlation between the C/M and the severity of LUTS. In the current study, LUTS severity was not evaluated because most patients had urinary retention. We did find an association between collagen deposition and the presence of DO as well as decreased compliance, both of which may be responsible for storage LUTS. These findings reinforce the concept that collagen deposition in the detrusor may be one of the mechanisms involved in the complex morphological, biochemical, and molecular alterations of the bladder that occur in association with BOO/BPH, and that ultimately lead to LUTS.[2]

The conflicting results regarding the association between detrusor collagen content and LUTS and/or urodynamic parameters are not surprising since the pathophysiology of LUTS/BPH is complex and involves many molecular mechanisms. Moreover, most studies are based on a relatively small number of patients who have overt BOO, which might prevent potentially relevant associations to be detected. Also, other factors may contribute, including differences in the patient population of the studies, sample size, age, duration and severity of LUTS/BPH, previous treatments, as well as duration and severity of obstruction. The bladder biopsy method and the staining technique might also add to the variability. Some studies obtained endoscopic bladder biopsies, which may provide sparse or absent representation of the detrusor muscle or coagulation artifacts of the specimens.[10,16] In the present study biopsies were obtained during open prostatectomy, which provided a satisfactory specimen in all patients. In addition, most researchers used trichrome staining to evaluate the deposition of connective tissue in the detrusor.[9,16] Trichrome staining is frequently used to assess connective tissue in the interstitium because it is practical, widely available, and inexpensive. However, it may not be sensitive at milder levels of fibrosis.[28] In the present study we used picrosirius red staining, which has been used to quantify collagen content in the bladder and different organs.[10,11,14] While more time-consuming and expensive than trichrome staining, it is highly specific for collagen fibers.[28]

The pathophysiological cascade that finally determines collagen accumulation is not clear. In the bladder, as in other organs, collagen deposition in the extracellular matrix is dependent on the activity of proteolytic enzymes, such as the matrix metalloproteinases (MMPs) and their endogenous inhibitors, the tissue inhibitors of metalloproteinases (TIMPs).[17] The latent form of MMP-1 has been shown to be responsible for collagen degradation in the bladder and TIMP-1, a glycoprotein that binds MMPs tightly, inhibits its activity.[17] Although this has not been investigated in men with BOO/BPH, Peters et al[17] have demonstrated decreased enzymatic activity of MMP-1 and increased levels of TIMP mRNA and protein in the ovine fetal BOO model. Backhaus et al[29] showed that MMP-1 was significantly down-regulated, while TIMP-1 levels were increased, in a time and pressure-dependent manner in an *in vitro* model of human smooth muscle cells under mechanical strain. Further research should elucidate the regulatory mechanisms involved in collagen homeostasis. Interestingly, recent evidences indicated that TIMPs may also be urine biomarkers and provide useful prognostic information in patients with neurogenic voiding dysfunction.[30] Sekerci et al[30], investigating 80 children with myelomeningocele, have shown that higher urinary TIMP concentration is associated with higher detrusor pressures as well as with renal scarring in renal scintigraphy.[30] Future research is warranted to define the usefulness of urinary biomarkers as diagnostic and/or prognostic tools in men with BOO/BPH.

The present study has a number of limitations that must be acknowledged. First, our control population was younger than the BPH group. The ideal control group should be an age-matched healthy sample of men without LUTS/BPH, which is very difficult to obtain. Interestingly, despite the younger age of our control group, their C/M ratio was higher than that of age-matched control groups from other series.[10,16] Another limitation is the fact that we did not evaluate the association between collagen deposition and severity of LUTS. Since our patient population was limited and many of our patients had urinary retention, we were not able to perform subgroup analysis. Finally, we did not have data on the postoperative follow-up of the patients. It would certainly be remarkable to evaluate the association between detrusor collagen deposition and surgical outcomes. A significant percentage of patients undergoing surgical treatment to relieve BOO/BPH remain with bothersome LUTS, which may result from morphologic and functional bladder abnormalities.[3,4] A better understanding of the cellular and molecular mechanisms involved in the failure of surgery to relieve BOO/BPH will be useful for patient selection and counseling before surgery, as well as for the development of new treatment strategies.

Men with BOO due to BPH have an increased and heterogeneous pattern of collagen deposition in the bladder smooth muscle layer compared to controls, which is associated with decreased bladder compliance, increased prevalence of DO, and urinary retention.

Conflicts of interest

All authors have no conflict of interest to declare.

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