

RELATIONSHIP OF PERIURETHRAL FIBROTIC IN BPH PATIENT WITH LUTS AND URINARY RETENTION

¹Zamroni, ¹Soetojo, ¹Sunaryo Hardjowijoto.

¹Department of Urology, Faculty of Medicine/Universitas Airlangga, Soetomo General Hospital, Surabaya.

ABSTRACT

Objective: Analyzing the differences between collagen thicknesses in periurethral region from transurethral resection of the prostate (TURP) specimens of Benign Prostate Hyperplasia (BPH) patients with lower urinary tract symptoms (LUTS) and of those with urinary retention. **Material & methods:** This was an observation analytic study on 30 patients who underwent TURP. Patients who met the inclusion criteria were divided into 2 groups: BPH patients with LUTS and those with urinary retention. Each group consisted of 15 people. The first TURP specimen of proximal verumontanum resection were examined in anatomic pathology using mass on strichrome staining as an examination of periurethral collagen thickness. Collagen will be stained as blue. Periurethral collagen thickness was measured from the basal membrane of transitional epithelium to fibromuscle tissue. Data were then statistically analyzed using independent t-test. **Results:** The average patient age was 66 ± 7 years old and there was no significant difference between age and periurethral collagen thickness with $p=0.175$ ($p>0.05$). The mean prostate volume was 47.19 ± 13.2 ml and there was no significant difference between prostate volume and periurethral collagen thickness with $p=0.148$ ($p>0.05$). Average periurethral collagen thickness in BPH patients with urinary retention was 146.67 ± 39.80 micrometers and while in those with LUTS was 205.33 ± 85.6 micrometers. There were no significant differences between periurethral collagen thickness and the occurrence urinary retention with retention of urine with $p=0.063$ ($p>0.05$). **Conclusion:** There were no significant differences between periurethral collagen thickness patients in BPH patients with LUTS and in those with urinary retention. This suggests that periurethral collagen thickness is not associated with the occurrence of urinary retention or LUTS in BPH patients.

Keywords: Periurethral fibrosis, collagen of periurethral, benign prostate hyperplasia.

ABSTRAK

Tujuan: Menganalisa perbedaan ketebalan kolagen periuretra prostatika hasil transurethral resection of the prostate (TURP) antara pasien Benign Prostate Hyperplasia (BPH) dengan lower urinary tract symptoms (LUTS) dan BPH dengan retensi urine. **Bahan & cara:** Penelitian adalah observasional analitik pada 30 pasien yang menjalani operasi transurethral resection of the prostate (TURP). Pasien yang memenuhi kriteria inklusi dibagi menjadi 2 kelompok yaitu BPH LUTS dan BPH retensi urine. Tiap kelompok terdiri dari 15 orang. Hasil spesimen TURP dari kerokan pertama di proksimal verumonyanum dilakukan pemeriksaan patologi anatomi dengan pengecatan mass on strichrome berupa pemeriksaan tebal kolagen periuretra. Kolagen akan berwarna biru. Ketebalan kolagen periuretra diukur dari membran basal epitel transisional sampai dengan jaringan fibromuskuler. Data dianalisa secara statistik dengan tes t-independent. **Hasil:** Rerata umur pasien 66 ± 7 tahun dan tidak terdapat perbedaan yang signifikan antara usia dengan tebal kolagen periuretra dengan $p=0.175$ ($p>0.05$). Rerata volume prostat 47.19 ± 13.2 ml dan tidak terdapat perbedaan signifikan antara volume prostat dengan tebal kolagen periuretra $p=0.148$ ($p>0.05$). Rerata tebal kolagen periuretra pada pasien BPH retensi urine adalah 146.67 ± 39.80 mikrometer dan rerata tebal kolagen periuretra pada pasien BPH LUTS adalah 205.33 ± 85.6 mikrometer. Tidak terdapat perbedaan yang signifikan antara tebal kolagen periuretra dengan terjadinya retensi urine dengan $p=0.063$ ($p>0.05$). **Simpulan:** Tidak terdapat perbedaan yang signifikan antara tebal kolagen periuretra pasien BPH LUTS dengan BPH retensi urine. Hal ini menunjukkan bahwa tebal kolagen periuretra tidak berkaitan dengan terjadinya retensi urine maupun LUTS pada pasien BPH.

Kata kunci: Fibrosis periuretra, kolagen periuretra, benign prostate hyperplasia.

Correspondence: Zamroni, c/o: Department of Urology, Faculty of Medicine/Universitas Airlangga, Soetomo General Hospital. Jl Mayjend. Prof. Dr. Moestopo 6-8, Surabaya 60286. Phone: +62 31 5501318; Fax: +62 31 5024971. Mobile phone: 081 335008830. Email: zamron_comal@yahoo.com.

INTRODUCTION

Benign Prostate Hyperplasia (BPH) is a benign enlargement of prostate gland with incidence up to 50% among 50-years-old men and increases with age. It is suffered by approximately 70% men aged over 60 years and 90% men aged over 80 years. Not all men with BPH suffered from clinical symptoms and the prevalence of symptomatic BPH in men aged 40-49 years reached almost 15%, increasing up to 25% in those aged 50-59 years and, at the age of 60, the prevalence were increasing to approximately 43%. Enlarged prostate is considered as a part of aging process, not differ from the graying hair and nowadays with the increase of life expectancy, so do the incidence of BPH.¹⁻³

BPH is a histopathological terminology characterized by the elevation number of stromal and epithelial cells of prostatic gland. Testes are external factors that highly contribute in the regulation of prostate growth since they produce 3 essential substances, such as testosterone, estrogen and non-androgenic testicular factors. Testosterone is metabolized in the nuclear membrane of prostate cells into dihydrotestosterone (DHT) by the enzyme of 5 α -reductase. DHT binds into the androgen receptor to form an androgen-receptor complex (DHT/AR) that bind a specific DNA in the cell nucleus led to an increase of gene transcription and stimulate the synthesis of growth factors protein that promote the growth of prostate cells. Two important components that cause bladder outlet obstruction (BOO) due to BPH are static component and dynamic component. Static components occurs due to enlargement of the prostate tissue itself. Dynamic component caused by the increase of smooth muscle tone of the prostate influenced by the autonomic nerves, particularly the sympathetic components.^{2,4,5}

Treatment of BPH has 2 objectives; reducing lower urinary tract symptoms (LUTS) using α -adrenergic blocker and preventing further enlargement by inhibiting 5 α -reductase. There were improvement of LUTS in approximately 80% patients using α -adrenergic blocker, while 17.4% patients remained refractory.⁶ Periurethral and periglandular fibrosis might have occurred and were responsible in those whose symptoms persisted.^{4,5} Fibrosis is a rigid and excessive growth of scar tissue caused by excessive deposition of extracellular matrix that includes fibroblasts, collagen and elastin. The stiffness of periurethral tissue will result in obstructive symptoms of LUTS. The more

periurethral collagens are, the more stiffness will occur, causing LUTS symptoms or urinary retention on top of that. To investigate that fibrotic process in prostate, we can examine the collagen thickness in prostatic part of periurethral region.⁴

OBJECTIVE

Analyzing the differences between collagen thicknesses in periurethral region from TURP specimens of BPH patients with LUTS and of those with urinary retention.

MATERIAL & METHODS

This study was conducted in Soetomo General Hospital Surabaya at 2014, and had a total sample of 30 patients and no patient were met a drop out criteria. Patients were divided equally into 2 groups, BPH patients with LUTS and those with urinary retention, consisting 15 patients in each group. All patients underwent TURP and their results of anatomic pathology were entirely benign prostatic hyperplasia (BPH). Inclusion criteria was as follows: 1). Patients suffered from BPH with LUTS (IPSS >7) and underwent TURP, 2). Patients suffered from BPH with urinary retention and underwent TURP, 3). PSA <4 ng/ dl, or if more should be confirmed having no malignancy on biopsy examination. Exclusion criteria was as follows: patients with clinical, laboratory and ultrasound (TRUS) likely lead to malignancy, PSA levels more than 4 ng/dl or patients whose histopathology result of 10-core biopsy showed malignancy.

Patients in both group were thoroughly examined, including history taking, clinical/physical examination, laboratory test and radiology examination. All TURP specimens were sent to anatomic pathology department to undergo histopathology review. In order to obtain the transitional epithelium of prostatic urethra in periurethral region, the first resection were taken from the medial lobe, proximal to verumontanum. Those first chips were then separated particularly into a bottle containing 10% buffered formalin. Periurethral collagen thickness was measured from the basal membrane of prostatic urethra deep into periurethral fibromuscle tissue. In mass on's tri-chrome staining, both basal epithelial membrane of prostatic urethra and collagen will be stained as blue.

Data was presented in descriptive and

analytic method, in the form of table. Initially data were tested using the Kolmogorov-Smirnov test, to check whether the data is normally distributed or not. If the data was normally distributed ($p>0.05$), it was then examined for hypothesis testing using independent t-test.

RESULTS

A total sample of 30 patients were divided into 2 groups equally, each consisted of 15 people. Characteristically, group of BPH patients with urinary retention had the youngest age of 52 years and the oldest of 83 years, with an average of 67 years; while the BPH patients with LUTS had the youngest age of 51 years old and the oldest of 78 years, with an average of 66 years. Overall, the youngest patient of both groups was 51-years-old

and the oldest was 83-years-old (table 1).

Based on age, BPH patients with urinary retention were mostly distributed in the group of 60-69 years, as many as 7 people (46.67%) while majority of BPH patients with LUTS were distributed in the group of 70-79 years by 7 people (46.67%). Overall the majority patients were in the age group of 70-79 years as many as 12 people (40%). Data were normally distributed with $p=0.567$ ($p>0.05$), showed no significant difference in patient age between study groups (table 2).

Prostate volume of BPH with urinary retention group was mostly distributed in the group of 50-59 ml, as many as 5 people (33.33%) with an average of 66.4 ml, while in BPH with LUTS group, majority of prostate volume was in the group 70-79 ml, as many as 5 people (33.33%) with an average of 45.25 ml. Overall prostate volume average was

Table 1. Description of patient age in both groups.

BPH	Age			Total
	Youngest (years)	Oldest (years)	Mean (years)	
Urinary retention	52	83	67	15
LUTS	51	78	66	15

Table 2. Description of patient based on age group.

BPH	Age (years, n=15)					ρ
	40-49	50-59	60-69	70-79	>80	
Urinary retention	0 (0)	2 (13.33)	7 (46.67)	5 (33.33)	1 (6.67)	0.567
LUTS	0 (0)	4 (26.67)	4 (26.67)	7 (46.67)	0 (0)	(66 $\pm$ 7)

Table 3. Description of patients based on prostatic volume groups.

BPH	Volume (ml, n=15)					ρ
	20-29	30-39	40-49	50-59	60-69	
Urinary retention	1 (6.67)	3 (20)	3 (20)	5 (33.33)	3 (20)	0.464
LUTS	3 (20)	2 (13.33)	3 (20)	5 (33.33)	2 (13.33)	(47.19 $\pm$ 13.2)

Table 4. Corellation of periurethral collagen thickness in BPH patients with urinary retention and in those with LUTS.

BPH	Thickness of periurethral collagen (mean, micrometer)	ρ
Urinary retention	146.67 $\pm$ 39.80	0.063
LUTS	205.33 $\pm$ 85.60	

47.19 ± 13.2 ml, with majority of prostate volume was distributed in the group of 50-59 ml, as many as 10 people (33.33%). Test data were normally distributed with $p=0.464$ ($p>0.05$), showed no significant difference in prostate volume between the two study groups (table 3).

Average periurethral collagen thickness in BPH patients with urinary retention was 146.67 ± 39.80 micrometers and while in BPH with LUTS

was 205.33 ± 85.60 micrometers. The difference test of periurethral collagen thickness between two groups had p value = 0.063 ($p>0.05$). It mean that there was no significant difference between periurethral collagen thickness between BPH patients with urinary retention and in those with LUTS. There was no significant relationship between the thicknesses of the periurethral collagen with the occurrence of urinary retention or LUTS in

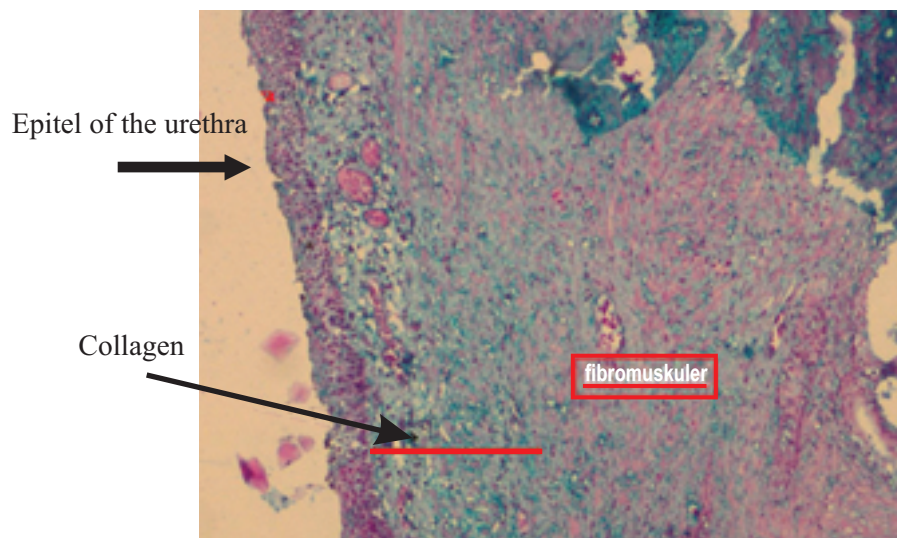


Figure 1. Periurethral tissue of BPH patients with LUTS in mass on'sthrichrome staining (100x magnification; collagen stained as blue, connective tissue stained as red).

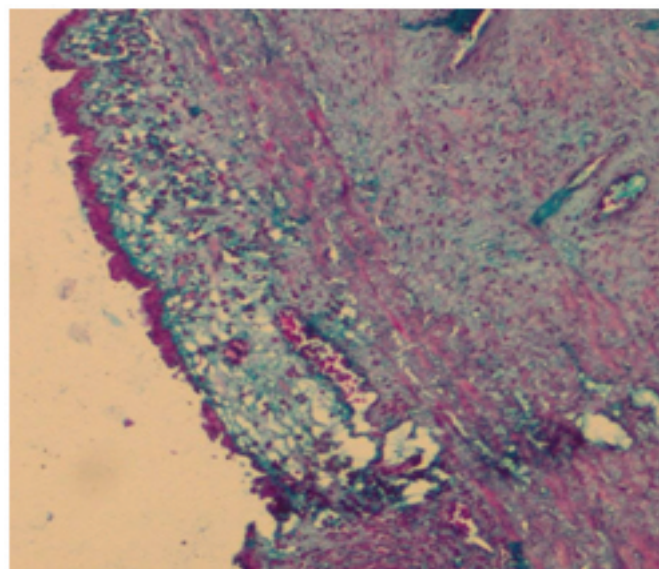


Figure 2. Periurethral tissue of BPH patients with urinary retention in mass on'sthrichrome staining (100x magnification; collagen stained as blue, connective tissue stained as red).

DISCUSSION

Fibrotic diseases covers a wide spectrum of diseases such as systemic sclerosis, scleroderma-tous and nephrogenic systemic fibrosis, as well as organ-specific disorders such as in lung, liver and kidney. The etiology and causes are varied. Those condition are related with an increased expression of the encoding gene of matrix protein, resulting in fibrosis which affect the associated organ and cause organ dysfunction or even failure. The production of extracellular matrix continuously activated by mesenchymal cells (myofibroblasts).⁷

The urethra has an elastic configuration. The content of prostatic/periurethral collagen were more in patients who has higher prostatic scores than in those with lower scores. Periurethral fibrosis can cause LUTS due to a decrease in urethral flexibility.^{4,5}

The results of this study showed no significant difference between periurethral collagen thickness in BPH patients with urinary retention and in those with LUTS. BPH patients with urinary retention were not proven to have thicker periurethral collagen compared to those with LUTS ($p=0.063$). This is not consistent with the research hypothesis suggesting that there is a difference between periurethral collagen thickness in BPH patients with urinary retention and in those with LUTS.

In this study there was no significant correlation between prostate volume and periurethral collagen thickness ($p=0.148$) and there was no significant relationship between age of patients with periurethral collagen thickness ($p=0.175$). It was consistent with the research from Jinjin Ma et al, which stated that the stiffness prostatic part of periurethral tissue is independent to prostate volume and the age of patient.⁴ Age of patients in this study were between 51 years old and 83 years old, with average age of 66 ± 7 years. Overall the majority of the patients were in the age group of 70-79 years, as

many as 12 people (40%).

CONCLUSION

There was no significant correlation between periurethral collagen thicknesses with the occurrence of urinary retention. Periurethral collagen thickness did not associate with the occurrence of LUTS or urinary retention in BPH patients.

REFERENCES

1. Roehrborn CG, McConnell JD. Benign prostatic hyperplasia: Etiologi, pathophysiology, epidemiology and natural History. In Walsh PC, Retik AB, Vaughan ED Jr., Wein A, eds. Campbell-Walsh urology, 10th Ed. Philadelphia: Elsevier Saunders; 2012. p. 2570–9.
2. Indonesian Association of Urologist. Guidelines of benign prostatic hyperplasia in Indonesia. Edited by Sunaryo Hardjowijoto, Akmal Taher, et al. Surabaya; 2003.
3. Nurdianto H, Alif S, Tarmono, Widodo JP. Perbedaan efikasi antara terapi intermitten doxazosin dan terapi harian doxazosin pada BPH yang disertai LUTS. Department of Urology, Medical Faculty/Airlangga University, Soetomo Hospital, Surabaya.
4. Jinjin Ma, Gharaee-Kermani M. Prostatic fibrosis is associated with lower urinary tract symptoms. *J Urol*. 2012; 188(4): 1375–81.
5. Cantiello F, Cicione A, Salonia A. Periurethral fibrosis secondary to prostatic inflammation causing lower urinary tract symptoms: A Prosp Cohort Study. Urology Unit and Doctoral Research Program, Magna Graecia University of Catanzaro, Italy. *J Urol*. 2013; 81(5): 1018–23.
6. Emberton M, Cornel EB, Bassi PF, Fourcade RO. Benign prostatic hyperplasia as a progressive disease: A guide to the risk factors and options for medical management. *Int J Clin Pract*; 2008. 10.1111/j.1742-1241.01785.x.
7. Rosenbloom J, Mendoza FA, Jimenez SA. Strategic for anti-fibrotic therapies. *Biochimica et Biophysica Acta*. 2013; 1832: 1088–103.