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The Thickness of Type I Collagen Fiber on Vaginal Wall Associated with The Degree of Anterior Pelvic Organ Prolapse

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ABSTRACT

Pelvic organ prolapse (POP) is estimated to affect almost 50% of women above the age of 50 years. However, the pathophysiology of prolapse is still unclear. This study aimed to analyze the correlation of the thickness of type I collagen fibers with the degree of anterior POP. The samples were divided into four groups; prolapse grade 0/I, grade II, grade III, and grade IV. The immunohistochemical staining was performed with type 1 collagen antibody to assess the thickness of type 1 collagen fibers using indirect immunoenzyme techniques. There was no difference in the age, parity, and menopause status of patients (P = 0.276; P = 0.984; P = 0.418, respectively) in all groups. Mean thicknesses of fibers of type 1 collagen patients with anterior POP in grade 0/I, II, III and IV were 3,634±0.0656 µm; 3,083±0.0174 µm; 2,585±0.0119 µm and 1,562±0.0922 µm, respectively. There was strong negative correlation between type 1 collagen fibers thickness and the degree of anterior POP (r = -0.969, p <0.0001). There was strong negative correlation between type 1 collagen fiber thickness and the degree of anterior POP.

Keywords: Pelvic organ prolapse, collagen type I, the vaginal wall

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INTRODUCTION

Pelvic organ prolapse (POP) often causes morbidity and lower quality of life of women. POP has a high prevalence. It has been estimated 50% of women who had give birth at least will have a POP. As many as 11% of women aged 80 undergo pelvic reconstructive surgery, and one-third of women with POP undergo more than one surgical procedure due to the recurrence of POP (1,2).

According to the Indonesian Demographic and Health Survey in 2012, life expectancy of women in the world and Indonesia in particular were increasing. They need their effort to maintain the quality of life of women who can be decreased as a result of long-term morbidity caused by childbirth. POP also has negative impacts on sexual function, appearance, and quality of life [1]. For the reasons of quality of life, POP is one of the indications for gynecological surgery. However, conservative management and lifestyle changes still play a role in the management of mild degree POP, people who still want to have children, or who do not want surgery (3).

The POP incidence was 35% in women over 40 years of age and is forecast to grow to 46%. In a multicenter observational study in the USA, POP incidence was found in 1004 women aged 18-83 years who performed routine prenatal prevalence of POP by POP-Q system as much as 24% (grade 0), 38% (grade 1), 35% (grade 2), and 2% (grade 3) (4). According to data from the Women's Health Initiative, prevalence of POP in women aged 50-79 years are distributed to 39.46% cystocele, 21.42% rectocele, and 16.3% uterine prolapse (5). Whereas, Indonesia had not reported the incidence of POP due to limited reporting system. In the study conducted by Nizomy, 371 cases of POP at gynaecologic clinic in Dr. Soetomo hospital during 2007-2011 were reported (6).

The anterior vaginal wall is the principal support for the bladder base. Cystocele or anterior vaginal wall prolapse is common in urinary incontinence, sexual dysfunction and discomfort [2]. This condition also may be caused by caesarean section and contribute for the development of urinary tract infections, which sometimes asymptomatic (7,8). Women with cystocele will decrease the quality of life significantly. Several studies that have been done suggest that changes in connective tissue is found in women with stress urinary incontinence and POP [3]. Howeve,r the underlying risk factors of POP vary, including a defect in the wall of the vagina itself or the supporting tissue structures, such as ligaments, fascia, muscles, and connective tissue of the pelvic floor (9).

Collagen is the principal element of the connective tissue of pelvic floor. Abnormal collagen metabolism has been identified related to the incidence of POP and stress urinary incontinence and still continues to be studied [4]. Some studies suggest that impaired synthesis and collagen types have causality in connective tissue disorders, such as POP and stress urinary incontinence. Remodeling continuous network makes the relationship between the synthesis and degradation of collagen very important to maintain the tensile strength of the connective tissue (10).

The mechanism of POP in women and the factors that led to the failure of the repaired scar are not yet fully understood.

There is some evidence to support that the connective tissue structure abnormalities are predisposing factors (11). Until recently, the researchers at Dr. Soetomo Hospital, Surabaya had never done study on the relationship between the thicknesses of Type I collagen fibers in the vaginal wall with the degree of anterior POP. The aim of this study is to measure the thickness of collagen type I fibers. This study is expected to know the relationship between type I collagen fiber thickness of the vaginal wall with the degree of anterior POP [5].

METHODS

This was an observational analytic and cross-sectional study. This study was conducted at Dr.Soetomo Hospital, Surabaya, Indonesia from October to December 2015. Samples were taken from the medical records of patients with abnormalities of the anterior pelvic prolapse who had undergo tranvaginal hysterectomy (TVH) or transabdominal hysterectomy (TAB). Sample were taken by consecutive sampling with a sample size of 28. The samples were then divided into four groups: prolapse grade 0/I, grade II, grade III, and grade IV. Then, the samples of paraffin blocks of the vaginal wall were taken at the Pathology laboratory Dr. Soetomo Hospital. The immunohistochemical staining was performed with type 1 collagen antibody to assess the thickness of type 1 collagen fibers using indirect techniques immunoenzyme.

After the measurement of type 1 collagen fibers, Kolmogorov-Smirnov normality test was done to check data distribution. If the data were normal distribution, the difference between groups was analyzed using one way Annova to observe the difference between the numerical variables. Furthermore, Pearson correlation test was done to assess correlation between the thickness of type 1 collagen and the degree of POP.

RESULTS

In all grades of POP patients, the age, parity and menopausal status are vary. Table 1 shows there is no difference in the age, parity, and menopause status of patients (P = 0.276; P = 0.984; P = 0.418, respectiveley) in all groups.

Table 1. Characteristics of study sample

Characteristics	Grades of anterior POP				p
	0/I (N = 7)	II (N = 7)	III (N = 7)	IV (N = 7)	
Age (years)	52.1 ± 3.9	58.8 ± 10.7	59.0 ± 8.0	58.1 ± 5.1	0.276
Parity	3.5 ± 2.3	3.2 ± 1.7	3.2 ± 0.4	3.2 ± 1.3	0.984
Menopause (%)	71.4	71.4	85.7	85.7	0.418

The paraffin blocks of vaginal wall were obtained in Pathology Laboratory of Dr. Soetomo hospital. Then, slides were made and stained by immunohistochemical with immunoenzyme indirect method using type 1 collagen antibody kit (NB 600-250, Novus Biological, USA) with a 1:100 dilution. Figure 1 shows that type 1 collagen fibers in the anterior vaginal wall POP patients are scattered around with fine lines and varying thickness grades. The fibers seemed more irregular and thicker with increasing degree of anterior POP.

The measurement of fibers thickness were made using microscope with software Leica Application Suite (LAS). Measurement of collagen fibers thickness in each slide was performed randomly five times with 400x magnification. In each field, five type 1 collagen fibers were measured in micrometer unit using LAS, then the average thickness of elastin fibers was calculated.

Table 2 shows that mean thicknesses of fibers of type 1 collagen in patients with anterior POP in grade 0/I, II, III and IV were 3.634±0.0656 µm; 3.083±0.0174 µm; 2.585±0.0119 µm, and 1.562±0.0922 µm, respectively. The results of p <0.0001 showed a significant difference.

Table 2. The thickness of type 1 collagen fibers between groups

POP Anterior	n	Average±SD	p
Grade 0/I	7	3,634±0.0656[a]	<0.0001
Grade II	7	3,083±0.0174[b]	
Grade III	7	2,585±0.0119[c]	
Grade IV	7	1,562±0.0922[d]	
Superscript different shows significant differences			

In this study, as a statistical test, *ANOVA brown Forsythes* showed significant differences, and the data were not homogeneous. Furthermore, the analysis of *post hoc Games-Howel* was performed to determine between which groups had significant differences. Based on analysis *post hoc* result, there was a difference of type I collagen fiber thickness between the anterior POP grade because the value of p <0.0001 with confidence interval 95%. Thus, there was a significant difference in type 1 collagen fiber thickness between each grade. These results indicated the thickness of type 1 collagen fibers significantly decreased as the degree of anterior POP arose.

Furthermore, to analyze the correlation between the thickness of type 1 collagen fibers and anterior POP, Pearson correlation test was done. There was strong negative correlation between type 1 collagen fiber thickness and the degree of anterior POP (r = -0.969, p <0.0001).

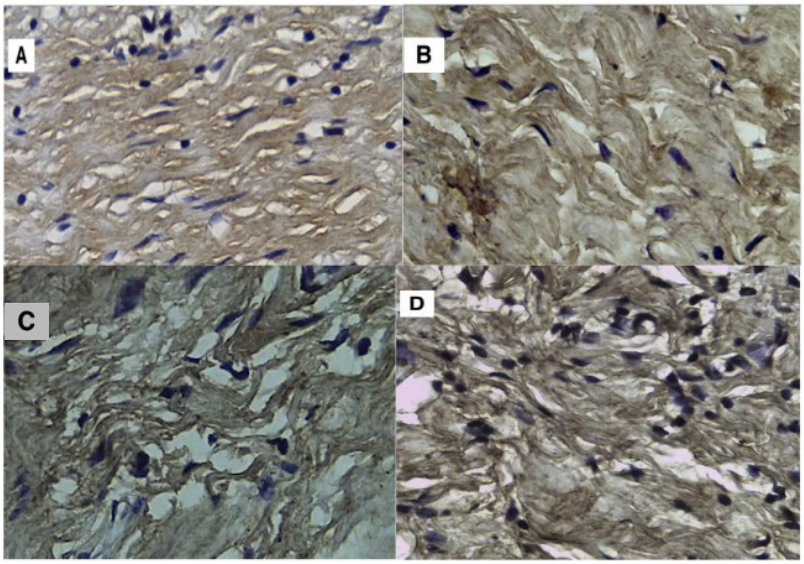

Figure 1: The results of immunohistochemical staining of type 1 collagen patients with anterior POP vaginal wall (magnification 400x): A. Degree 0/I, B. Grade II, Grade III and D. C. Degree IV.

DISCUSSION

There was significant difference in all groups and association between thickness of the type 1 collagen fiber and the degree of anterior POP. The thickness of type 1 collagen fibers in the vaginal wall decreased with the increasing anterior POP degree.

Age is a major factor affecting the degree of uterine prolapse with the main cause in weakening of pelvic floor tissue and muscle in elderly women (12). The mean age of patients increased with grade of anterior POP in this study. This finding is consistent with several previous studies that the incidence of POP increases with ages. POP occurs in half of women aged 50 years and older with a prevalence reaching 30-50% (13). Another study reported the risks of uterine prolapse, rectocele, cystocele increase with ages. Women aged 60 to 69 years had an *odds ratio* (OR) of 1.16 times for uterine prolapse compared to women aged 50-59 years and women aged 70-79 years who had an OR of 1.36 times to occur POP (14). Other studies also stated the results are not different, wheater the incidence and prevalence of POP increase with age. As the age increases, the connective tissue will decrease the flexibility and ability to support pelvic organs causing POP (5,6).

Pregnancy and childbirth are major risk factors for the occurrence of POP. Levator ani muscles and endopelvic fascia play important role to maintain the pelvic organs. However, both structure can be injured during the process of pregnancy and childbirth, leading to POP. The cohort study in Sweden conducted on 487 women reported the risk of POP increases with parity and age. Women who have given birth one time will experience a risk of POP as much as two-fold compared to nulliparaous woman (15).

Vaginal delivery and increased parity are risk factors that mostly contribute to the occurrence of POP because the process of vaginal delivery can cause trauma to the pelvic floor structure. Birth trauma can occur in the structure of muscles, fascia, ligaments, and nerves through the mechanism of the stretch, tear, or direct injury to the nerve fibers. These processes lead to weakness of the pelvic floor and pelvic floor dysfunction that underlie the emergence POP. The more deliveries, the more the risk and the possibility of birth trauma (16).

Women who do not receive hormone replacement therapy have a higher risk of POP, and the use of hormone replacement therapy more than 5 years will reduce the risk of POP (17). Other reports said the starting age of menopause is associated with POP symptoms (18). Menopause leads to a decrease in estrogen levels (19). The fascia and connective tissue of pelvic floor lose strength along with the aging process. Estrogen deficiency can affect the quality and quantity of collagen composition because of its defense against oxidative stress (20). Estrogen affects the collagen content by increasing or decreasing the synthesis of collagen degradation. It is said that exogenous estrogen supplementation can increase collagen content in the skin of postmenopausal women (21).

The thickness of type 1 collagen fibers is associated with anterior POP degrees. This finding is consistent with previous study. In POP group, the type I collagen fibers are thinner when compared with the group without POP (22). The earlier study also showed significant differences in the expression of type I collagen and decreased expression of collagen type I in POP patients compared to patients without POP (23).

The disturbance of extracellular matrix protein, especially collagen, is degraded by matrix metalloproteinases (MMPs) (24), and MMP-1 is the interstitial collagenase owned by the primary substrate collagen types I, II, III, IV. MMP-1 contributes to the degradation of collagen, and the increase of the activity of MMP-1 leads to a reduction of collagen. A study with a biopsy of the vaginal wall found increased expression of MMP-1 mRNA in women with POP and decreased expression of Tissue inhibitors of metalloproteinase type-1 (TIMP-1) mRNA (25). Besides,

study on 46 women with POP and 49 women without POP compare the expression of type I collagen and MMP-1 in the uterosacral ligaments. There are decreased expression of type I collagen and increased expression of MMP-1 in the POP group compared to the group without POP (26). A decrease in collagen is found in women with POP and stress urinary incontinence compared to women without POP, showing a decrease in total collagen in pubocervical fascia (27).

It is more objective to measure the thickness of type 1 collagen. Increase in type I collagen degradation is mechanical response due to mechanical stress on the vagina during childbirth. Childbirth may damage the levator ani muscle and connective tissue, causing an increase in intra abdominal pressure on the vaginal wall. These increases the mechanical load on the vaginal wall and increases the strain on the tissue. Increased mechanical load itself has been known to increase the activity of tissue remodeling one of them by increasing the activity of MMPs by fibroblasts in the vaginal wall which can degrade type I collagen fibers, to obtain a thickness reduction of type I collagen fibers causing POP.

From this study, the quality and quantity of type I collagen fibers play a role in maintaining the strength of the pelvic floor, with decreasing thickness of the collagen fibers occurs weakness in the connective tissue of the pelvic floor prolapse, which may occur. Collagen density in patients with uterine prolapse is lower compared with patients with non prolapse (28-33).

In this study, there is a limitation such as sampling of vaginal wall during Total abdominal hysterectomy (TAH) surgery for POP grade 0/1 due to difficulty to gather more specimen. Also, there is difficulty to identify another risk factor that increases abdominal pressure, such as obesity, chronic cough, and constipation due to uncomplete medical record.

CONCLUSION

The thickness of the type 1 collagen fiber was associated with the degree of anterior POP. There was strong negative correlation between type 1 collagen fibers thickness and the degree of anterior POP.

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