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Changes type III collagen expression in human uterosacral ligaments of uterine prolapse

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Abstract: There are some controversies regarding the content of type III collagen fibers in uterosacral ligaments in pelvic organ prolapse (POP). The role of these fibers is still unclear. This study aims to compare the content of type III collagen fibers in uterosacral ligaments (USL) in patients with or without POP. This is a cross-sectional analytic study conducted in 23 women with POP from Jakarta Indonesia. The study took place in Dr. Hasan Sadikin Hospital during May-October 2011. The type III collagen fiber content in USL of women with POP was 50% higher than those in women without POP (p=0.036). In conclusion, the type III collagen fibers content in USL of women with POP is more dense compared with those without POP.

Key words: Type III collagen fibers; Pelvic organ prolapse; Uterosacral ligaments.

INTRODUCTION

Gabriel et al found that there were strong immunohistochemistry reactions of type III collagen fibers in uterosacral ligament (USL) in women with pelvic organ prolapse (POP) compared with type I and type II collagen fibers. Jackson also found that there was reduction of collagen amount with predominately immature collagen content in women with POP and cystocele, compared with those without POP.

In women with POP, there were several changes in cell transcription program in USL, leading to changes in matrix production, mechanical properties, cell shape, inflammatory reaction, and healing process. Furthermore, the immature collagen content also relatively higher.

The study regarding type III collagen fibers in USL of women with POP has been widely conducted worldwide, but mainly in Caucasians. The data from Asian women is still scarce. This is the first study comparing type III collagen fiber content in USL in Indonesian women.

MATERIAL AND METHODS

This is a cross-sectional analytic study, conducted in Dr. Hasan Sadikin Hospital Bandung during May-October 2011. Subjects were women with grade 2, 3 and 4 POP, while the control group was women without POP or with POP grade 1 served as control group. The characteristics of subjects may be seen in table I. There were significant differences in age and menopausal status between POP group and control group (p<0.05), while parity and BMI were not significantly different (p>0.05). No subject had received hormone replacement therapy. Most of POP subjects had grade 3 POP (62.5%), followed by grade 2 (26.1%), and grade 4 (8.7%). There were no grade 1 POP subjects in this study.

RESULTS

The study was conducted during a six-month period, from May-October 2011. During that period, all subjects fulfilled inclusion criteria were enrolled to this study. There were 23 women with POP, and 23 women without POP or with POP grade 1 as control group. The characteristics of subjects may be seen in table I. There were significant differences in age and menopausal status between POP group and control group (p<0.05), while parity and BMI were not significantly different (p>0.05). No subject had received hormone replacement therapy. Most of POP subjects had grade 3 POP (62.5%), followed by grade 2 (26.1%), and grade 4 (8.7%). There were no grade 1 POP subjects in this study.

TABLE I. - Subject characteristics (n=46)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Pop (n=23)</th>
<th>Control (n=23)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Age Mean (SD):</td>
<td>50.2 (9.2)</td>
<td>62.4 (7.8)</td>
<td>0.001**</td>
</tr>
<tr>
<td>2. Menopausal status</td>
<td>21 (43.5%)</td>
<td>12 (26.1%)</td>
<td>0.001**</td>
</tr>
<tr>
<td>Premenopause</td>
<td>21 (45.7%)</td>
<td>11 (23.9%)</td>
<td></td>
</tr>
<tr>
<td>Postmenopause</td>
<td>0.005***</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Parity Median</td>
<td>4</td>
<td>0.645**</td>
<td></td>
</tr>
<tr>
<td>Range: 2-12</td>
<td>0-8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. BMI (kg/m²) Median</td>
<td>21.21</td>
<td>20-27.77</td>
<td>0.095***</td>
</tr>
</tbody>
</table>

The comparison of distribution and intensity of type III collagen fibers between POP and control group may be seen in figure 2a, 2b. The median of type III collagen fibers distribution was significantly higher in POP group (p<0.05). The intensity of type III collagen fibers was higher in POP group as well but not significantly different with the control group (p>0.05).
The comparison of Histo Score between two groups may be seen in figure 3. There was a significant difference of Histo Score between POP and control group (median 12, range 3-16 vs median 8, range 1-16, p<0.05). There was no significant correlation between degree of POP and type III collagen fiber content (p>0.05). Furthermore, there were no significant correlations between age and menopausal status to type III collagen fiber content, as seen in table 3 and figure 4.

DISCUSSION

Although the exact pathophysiology of POP is still unknown, there are some risk factor contributing in the occurrence of POP, i.e pregnancy, vaginal delivery, age, elevation of intrabdominal pressure, menopause, hypoestrogenic status, trauma, genetic factor, race, musculoskeletal disorders, chronic debilitating illness, smoking, and previous history of surgery. From previous studies, mechanical and metabolical changes in connective tissue may serve as predisposing factors for POP. Furthermore, the reduction of collagen fiber amount as well as decreasing quality of those fibers also may contribute in POP.

According to WHI study, there are higher risks in older women to develop POP (1.2 times higher in women aged 60-69 years, and 1.4 times higher in women aged 70-79 years compared with those whose aged 50-59 years). In a cross-sectional study of 21,449 menopausal women in Italy, the risk of POP in older women are higher compared to younger women. The risk of POP in women aged 60-69 years is 1.4 times higher compared with those whose aged 50-59 years. Furthermore, the reduction of collagen fiber amount as well as decreasing quality of those fibers also may contribute in POP.

Table 2. - Effect of degree of POP on the content of type III collagen fibers.

<table>
<thead>
<tr>
<th>Degree of POP</th>
<th>Mean Rank Histo Score of type III collagen</th>
<th>N</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degree 2</td>
<td>14.33</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Degree 3</td>
<td>10.93</td>
<td>15</td>
<td>0.535</td>
</tr>
<tr>
<td>Degree 4</td>
<td>13.00</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

Table 3. - The influence of age on the content of type III collagen fibers.

<table>
<thead>
<tr>
<th>Age Classification (years)</th>
<th>Mean Rank Histo Score of type III collagen</th>
<th>N</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-39</td>
<td>15.25</td>
<td>2</td>
<td>0.547</td>
</tr>
<tr>
<td>40-49</td>
<td>10.93</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>50-59</td>
<td>20.00</td>
<td>15</td>
<td>0.535</td>
</tr>
<tr>
<td>60-69</td>
<td>25.58</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>70-79</td>
<td>25.42</td>
<td>6</td>
<td>0.547</td>
</tr>
</tbody>
</table>
Changes type III collagen expression in human uterosacral ligaments of uterine prolapse

Comparison of type III collagen in POP and without POP

Increased content of type III collagen fibers that play a role in tissue elasticity and elongation tissue will lead to decrease ratio in the content type I: III of collagen fibers, which will produce tissue laxity.4

The median histological score of type III collagen fibers in the uterosacral ligaments POP women in this study was 50% higher compared to women without POP (p < 0.05), the situation has been implicated in the occurrence of POP. The high content of type III collagen fibers to women with POP in this study was not sufficient evidence of an increasing in the content of type III collagen fibers because this study is cross-sectional.

The results in this study are in accordance to study conducted by Gabriel et al.1 who showed that the content of type III collagen fibers was significantly higher in uterosacral ligaments in patients with POP. They suggested that the content of smooth muscle in uterosacral ligaments about 20% and collagen type I in the uterosacral ligaments almost the same between postmenopausal women with and without POP, but the content of type III collagen was significantly increased for uterosacral ligaments in patients with POP. Suzme et al.11 found that the hydroxyproline levels decreased in uterosacral ligaments women with POP although in histopathology seen an increase in collagen density. Collagen synthesis in women with POP is increased in fibroblasts compared to controls. It shows that the mRNA of collagen types I and III increased. The newly formed immature collagen is more susceptible to endogenous proteases and therefore is unlikely contribute to mature cross-linked collagen that confers strength and durability connective tissues.4

Connell et al.12 found that the expression of both collagen type I and collagen type III was significantly reduced 7.3- and 17-fold in the uterosacral ligaments of women with POP compared with controls, due to decrease in procolla-

Figure 3. - Comparison of content of type III collagen fibers in women with and without POP.
Statistical analysis using Mann-Whitney U nonparametric test.

Women who experienced vaginal delivery have a higher risk of developing POP compared to nulliparas (8.4 and 10.9 times higher for twice and four or more deliveries respectively; 95% CI 4.7-33.8)8 According to Bradley et al.4 women who experienced 1-2 times vaginal deliveries have 1.28 (0.49-3.32) cm vaginal descent; while in women who have 3-4 and more than 5 vaginal deliveries the vaginal descent was 2.35 (0.98-5.67) cm and 4.82 (1.92-12.09) cm respectively. In this study, mean parity was 4 (range 2-12). In our group, high parity is a major factor for POP incidence. In contrast with this condition, in western countries POP may be found in the low parity group. Furthermore, we also found women with low parity group as well.

Increasing BMI also play a role on the incidence of POP. Women who are overweight (BMI 25-30 kg/m²; OR 2.51, 95% CI 1.18-5.35) and obese (BMI> 30 kg/m²; OR 2.56, 95% CI 1.23-5.35) are at high risk of developing POP.8 Some studies suggest an association between POP and increased BMI, but other studies did not find a correlation between the POP and the increase in BMI, so the correlation of the two variables is still a controversy.6 BMI in this study is still considered within normal limits, so the subject’s BMI in this study did not include a risk factor for POP. The higher the BMI, the higher the risk of POP, but with the thought that obese women have higher estrogen level will reduce the risk of incidence of POP. The study specifically to determine the correlation between POP and BMI as confounding factors has not exist, therefore, the opinion is still a matter of controversy among researchers.

Most women with POP in this study were postmenopausal and had received no hormone replacement therapy. These are risk factors for POP.
REFERENCES


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