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COLLAGEN III AND MATRIX METALLOPROTEINASE (MMP) 9 IN CERVICAL ELONGATION AND PELVIC ORGAN PROLAPSE: A NARRATIVE REVIEW

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Abstract
Cervical elongation is an extension or hypertrophy of the cervix towards the introitus with the supporting tissues of the uterus still in good condition. Knowledge regarding the pathogenesis of cervical elongation is still unclear. This review discusses cervical elongation and its association with the expression of collagen III and MMP 9. We searched for literature in the last five years through Google Scholar, PubMed, and Science Direct databases. Cervical elongation is a phenomenon that occurs when the cervix is longer than normal and is a co. Common but poorly defined problem in gynecology. Cervical prolongation is associated with efforts to manage patients with pelvic organ prolapse. Various studies reveal that there is a chance that collagen 3 and MMP-9 are associated with the incidence of cervical elongation. However, further research is still needed to find more specific and accurate results. Collagen is a fibrous protein that provides tensile strength to the skin, tendons, and bones. Changes in collagen content and structure can destroy the supporting function of the pelvic floor, which can lead to POP. Matrix metalloproteinase-9 (MMP-9) is a protease associated with the degradation of collagen and elastin. Increased activity of MMP-9 in vaginal tissue has been associated with pelvic organ prolapse.
Keywords: MMP-9, Collagen III, pelvic organ prolapse, cervical elongation, cervical tissue

INTRODUCTION

Pelvic Organ Prolapse (POP) is the descent of the pelvic organs caused by the weakening of the supporting structures of the pelvic organs. This results in protrusion of the uterus or cervix through the vagina. POP can be classified as anterior, posterior, apical prolapse, or vaginal stump prolapse (1). Research conducted by the Women's Health Initiative on 27,342 menopausal women found that the prevalence of POP was 41.1% for women who still had a uterus and 38% for women who did not have a uterus (2). The prevalence of POP in low-income countries such as Tanzania, Ethiopia, and Gambia is 46-64.6% (3). In Indonesia, Bandung reported 30 cases of grade III-IV prolapse in Bandung during 2007 and in Bali, there were about 20 cases of III-IV degree prolapse each year (4). In the Central General Hospital (RSUP) Ciptomangunkusumo there were 252 cases of POP in 2016-2018 with a prevalence of 15.96% (5).

Not all patients with uterine prolapse have a decreased corpus uteri, as occurs in cervical elongation (6). Cervical elongation and POP cases can cause persistent problems. Cervical elongation is an extension or hypertrophy of the cervix towards the introitus with the supporting tissues of the uterus still in good condition (7). Cervical elongation can occur in both parts of the cervix, namely the supravaginal part and the vaginal part. Supravaginal cervical elongation is found in 18% of patients with POP, whereas vaginal cervical elongation almost always occurs congenitally (8). Knowledge of the pathogenesis of cervical elongation is still unclear, so further research is needed (9).

There is some suggestion that abnormalities in the composition of connective tissue contribute to cervical elongation. Previous research found decreased expression of type I collagen and increased expression of type III collagen in the uterosacral ligament of women with POP compared to non-POP (10). Decreased expression of type III collagen may play an important role in determining the physiology and structure of uterine prolapsed uterine cervical tissue. (11). In addition to type III collagen, matrix metalloproteinase (MMP) plays an important role in tissue remodeling associated with various physiological or pathological processes such as morphogenesis, angiogenesis, tissue repair, cirrhosis, arthritis, and metastasis. Protein expression and mRNA levels of MMP2 and MMP9 were significantly higher in the POP group. (12). Another study found that a significant correlation existed in the expression of pro-MMP-2, activating MMP-2, MMP-9, and TIMP-2 in vaginal tissue with it in the uterosacral ligament. (13).

Previous studies have not compared collagen III and MMP 9 levels in cervical elongation, but are still examining prolapse and non-prolapse comparisons. This review discusses cervical elongation and its association with the expression of collagen III and MMP 9, to pelvic organ prolapse.

Overview

Cervical Elongation

Cervical lengthening is a phenomenon that occurs when the cervix is longer than normal and is a common but poorly defined problem in gynecology. There is no consensus on the definition of cervical elongation, but some studies have used criteria such as Berger's Definition which states the length of the cervix is greater than 33.8 mm, the length of the cervix is more than 5 cm between the internal and external cervical ostium (14), and MRI results showed 3.38 cm above average for a non-prolapsed population (15). Some risk factors associated with cervical elongation include older age, BMI greater than 30, diabetes, vaginal delivery, larger cervical diameter, and a history of smoking. CE is associated with pelvic organ prolapse (POP). A study found that women with symptomatic POP had a higher ratio of cervical length to total uterine length than women without POP (16).

Today, gynecologists face challenges when approaching patients with what is defined as "cervical extension". It has a major role in treating pelvic organ prolapse, but understanding is still limited. During the preoperative examination, the surgeon must identify the presence of cervical elongation, as it affects the surgical procedure of choice and the outcome, taking Manchester surgery as an example – a procedure that involves shortening the cervix and attaching a stump to the uterosacral ligament. The failure rate for this procedure varies between 0-50%, whereas when focusing on cases involving only cervical elongation prolapse (the 'D' point on the intact POP-Q), the failure rate is 0%. Cervical lengthening hurts the success of performing concomitant salpingo-oophorectomy associated with increased operative time during secondary vaginal hysterectomy due to difficulty reaching the anterior and posterior fornix. Cervical lengthening is consistently associated with good posterior vaginal apical support and a well-supported dead end, but they also state that the exact mechanism remains elusive. (17). CE is associated with a statistically significant increase in operative time in women undergoing hysterectomy at the time of prolapse repair. (15).

It is generally believed that pelvic organ prolapse (POP) is associated with cervical lengthening. However, cervical length has not been officially compared between women with prolapse and those with normal support. About 40% of women with prolapse have cervical elongation; 57% of cervical elongation in prolapse can be explained by logistic regression-based models including POP-Q C point, body mass index, and menopausal status. Cervical lengthening is found in one-third of women with POP, with the rate of elongation increasing with greater rates of uterine decline. (18). Lower parity and advanced uterine prolapse are predictors of cervical elongation in women with uterine prolapse. Thus, uterine prolapse stage ≥3 or logit(p) ≥-0.18 may be useful for predicting cervical elongation (19).

Collagen III

Collagen is a fibrous protein that provides tensile strength to the skin, tendons, and bones. Changes in collagen content and structure can destroy the supporting function of the pelvic floor, which can lead to POP. Research on collagen changes at the pelvic floor is limited and controversial. More research is needed to better understand the role of collagen in POP. Type III collagen expression and low I/III collagen expression ratio are associated with pelvic organ prolapse (POP). One study found that women with POP had higher levels of type III collagen expression than women without POP. Another study found that women with POP had lower I/III collagen expression ratios than women without POP. Strong expression of type III collagen was more common in the group with POP (84.8%) compared to the group without POP (58.8%) (20).

Collagen is a fibrous protein and a major component of connective tissue. It provides tensile strength to the skin, tendons, and bones. Types I, III, and V are the main components for providing strength to the soft tissues. Type I collagen is inelastic and provides great resistance to tensile forces, whereas type III collagen has elastic properties and applies to more flexible tissues. Type I and III collagen is present in the granulated tissue during wound repair. An increase in type III and V collagen is associated with a decrease in the mechanical strength of connective tissue due to a decrease in fiber size. It is generally agreed that a higher ratio of I to III in the network indicates greater strength, while a lower ratio may result in network laxity (21).

Pelvic organ prolapse is a group of diseases caused by weakened pelvic supporting tissue, but its pathophysiology is not fully understood. Collagen is one of the most important components of the extracellular matrix in connective tissue, as it maintains the supporting function of the pelvic floor. Collagen I and III are the two main subtypes of pelvic tissue. With conflicting results from different studies, changes in content and ratios are still debated. The small sample size and different recruitment criteria, biopsy locations, and research methods make comparisons between different studies difficult. More research on collagen changes is needed to better understand the pathogenesis of pelvic organ prolapse (22). The study was conducted on 36 specimens of cervical tissue obtained at the time of surgery from 16 postmenopausal women with uterine prolapse (stage III-IV with pelvic organ prolapse quantification examination) and 20 postmenopausal women without uterine prolapse (control group). The cervix is longer in patients with uterine prolapse than in postmenopausal control without uterine prolapse. The ratio of type III and type I collagen in cervical tissue decreased significantly in the prolapsed uterus, compared to the postmenopausal cervical cervix without prolapse. These results suggest that decreased expression of type III collagen may play an important role in determining the physiology and structure of cervical tissue uterine uterine prolapse (11). Severe prolapse is associated with stiffer collagen fibrils, reduced collagen D periods, increased fibril alignment, and imbalanced collagen synthesis, degradation, and sedimentation. In addition, the progression of prolapse appears to be synchronized with collagen matrix damage, suggesting that POP-Q scores obtained through non-invasive clinical tests could potentially be used to quantitatively assess collagen abnormalities from the patient's local tissues (23). Women with symptomatic POP have a much higher ratio of cervical length to total uterine length than women without POP (24).

Metalloproteinase (MMP) matrix 9

Matrix metalloproteinase-9 (MMP-9) is a protease associated with the degradation of collagen and elastin. Increased activity of MMP-9 in vaginal tissue has been associated with pelvic organ prolapse. Matrix metalloproteinase-9 (MMP-9) is a biologically plausible candidate gene for pelvic organ prolapse. A Study by Budatha et al. showed that the origin of prolapse in

mouse models was related to the relationship between MMP-9 and fibulin-5, proteins that are essential for the development of normal elastic fibers. They found that 96% of mice with fibulin-5 knockout had a prolapse due to increased MMP-9 activity and impaired elastogenesis. In humans, some studies have shown that MMP-9 activity is higher in the vaginal tissues of women with prolapse compared to those without prolapse. Limited data exist on the impact of genetic variants on genes encoding the MMP-9 protease and the risk of pelvic organ prolapse in humans (25). Matrix metalloproteinase is responsible for breaking down collagen, but TIMP prevents MMP from doing its job. In women with POP caused by collagen tissue damage, MMP-9 showed the greatest improvement. To maintain fibroblast and collagen health in postmenopausal women, increased MMP-9 expression and decreased TIMP-1 expression are necessary, which results in a decrease in the incidence of POP. The expression of MMP-9 in prolapsed patients was significantly higher than in control patients. In addition, the level of TIMP-1 expression decreased significantly in prolapsed patients. Impairment of ECM balance is caused by increased expression of MMP-9 and decreased expression of timp-1, leading to clinical signs of pelvic organ prolapse (26).

A study aimed to investigate the possible relationship of increased matrix metalloproteinase (MMP)-1,-9 with pelvic organ prolapse (POP) and to evaluate whether the inflammatory process contributes to its development. Forty women who underwent Hysterectomy, 20 with POP grade 2 and above, and 20 without POP, participated in the study. Biopsy of the uterosacral ligament and vaginal mucosa is obtained from every woman. Each biopsy was cut and stained for MMP-1 and MMP-9 by immunohistochemical methods and by Hematoxylin and Eosin (H&E). MMP-1 and -9 expression was evaluated on immune-stained slides. H&E-stained parts are checked for possible inflammatory changes. MMP-1-9 expression appears to be increased in the tissues of women with POP. This supports an association, though not a cause-and-effect relationship, between the increase in MMP-1,-9, and POP. (27).

Studies on extracellular matrix (ECM) changes in pelvic organ prolapse (POP) are still controversial. A review found thirty cross-sectional studies were included, consisting of 840 POP cases and 755 controls. The overall results showed that the expression of collagen type III (COLIII) and some matrix metalloproteinases (MMP-1, -2, and -9) was increased, while collagen type I, and matrix tissue inhibitors metalloproteinase-1 (TIMP-1) decreased in patients with POP. Subgroup analysis showed that the expression of COLIII on the anterior vaginal wall (AVW) and COLIII, MMP-2, and -9 on the uterosacral ligament (USL) was consistent with overall results. However, expression and MMP-1 in AVW do not show any difference, and expression and MMP-1 in USL are still controversial based on current research. Patients with POP have lower expression and TIMP-1 and higher expression of COLI and MMP compared to non-POP cases, but more research is needed to investigate specific anatomical sites (28).

Conclusion

Cervical elongation is a phenomenon that occurs when the cervix is longer than normal and is a common but poorly defined problem in gynecology. Cervical prolongation is associated with efforts to manage patients with pelvic organ prolapse. Various studies reveal that there is a chance that collagen 3 and MMP-9 are associated with the incidence of cervical elongation. However, further research is still needed to find more specific and accurate results.

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