REVIEW

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The role of matrix metalloproteinase-9 (MMP-9) and tissue inhibitor of metalloproteinase-1 (TIMP-1) Expression in pelvic organ prolapse: A literature review

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ABSTRACT

Menopause is a physiological process as women get older. Urogenital syndrome, sexual difficulties, and pelvic organ prolapse (POP) are all common complaints among postmenopausal women, and these conditions can negatively impact their quality of life. There are still many unknowns regarding the pathophysiology and mechanisms of POP. Pelvic organ prolapse has been linked to the equilibrium of the extracellular matrix (ECM), which is controlled by matrix metalloproteinases and tissue inhibitors of metalloproteinases. Menopausal women experience a variety of symptoms due to hormonal changes, from urinary tract disturbance, vaginal atrophy, vaginal shortening, up to genital prolapse. Due to the collagen's diminished contractility, POP happens. Matrix metalloproteinase is responsible for breaking down collagen, but TIMP prevents MMP from doing its job. In women with POP caused by the breakdown of the collagen network, MMP-9 exhibits the greatest rise. In order to preserve the health of fibroblasts and collagen in postmenopausal women, increased expression of MMP-9 and decreased expression of TIMP-1 are necessary, which results in a decreased incidence of POP. The expression of MMP-9 in prolapse patients was significantly higher than control patients. In addition, TIMP-1 expression levels were significantly decreased in prolapse patients. Damage to the ECM's equilibrium is caused by increased MMP-9 expression and decreased expression of timp-1, which leads to clinical signs of pelvic organ prolapse.

Keywords: Pelvic organ prolapse (POP), MMP-9, and TIMP-1.
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INTRODUCTION

Menopause is a phase in a woman's life when menstruation stops permanently for 12 months due to estrogen deficiency and is not related to pathological causes.[1] Even though menstruation is a physiological condition, menopausal women have a variety of symptoms due to hormonal changes, such as decreased libido, dry vagina, sleeplessness, sadness, anxiety, and changes in urogenital anatomy. Following menopause, low estrogen levels lead to urinary tract issues (urinary retention, incontinence, etc.), genital prolapse, genital atrophy, vaginal constriction and shortening.[2] According to research, 40% of women have pelvic organ prolapse, 90% of women complain about sexual difficulties, and 93% of women complain about urogenital syndrome.[3] The pathogenesis of POP is complicated; in general, it is a reaction of the pelvic connective tissues and pelvic floor muscles to long-term pressure or laceration, or cell metabolic changes. As a result, the connective tissues of the pelvic floor are damaged, and the elasticity of the pelvic floor muscles is weakened, leading to muscle relaxation and damage.

Fibroblasts, collagen, and elastin are significant components of the connective tissue of the pelvis. Collagen production in the pelvis is significantly influenced by estrogen. One of the primary components of connective tissue in the pelvis is collagen. Changes in fibroblasts can lead to changes in collagen.[4] Collagen I and III are mostly produced by fibroblasts, whereas MMP-1, -2, -8, -9, and -13 (Matrix Metalloproteinase) break down collagen. To achieve a balanced state for the extracellular matrix, TIMP (Tissue Inhibitor Metalloproteinase) is an MMP inhibitor. MMP-9 is the MMP type that exhibits the greatest rise in women with pelvic organ prolapse as a result of deterioration of collagen tissue integrity.[5]

Vaginal Anatomy and Histology

Vagina is a fibromuscular tube located dorsal to the urethra and ventral to the rectum. The vagina consists of the vestibule, which is the outer part of the vagina, and the posterior vagina which is from the opening of the uterus to the cervix.[6] The pelvic fascia's tendinous arches, which run bilaterally from the pubis to the ischial spines, are where the lateral walls of the vagina are connected to the internal

obturator muscles. The rectovaginal fascia also has attachments to the arch tendinous. Support is given to the middle part of the vagina by these attachments. The cardinal-uterosacral complex supports the endopelvic fascia, which connects with the cervical fascia in the superior region. Levator ani and Luschka's fibers support the inferior portion of the vagina (fibers of the pubococcygeus muscle) and via attachments to the perineal body and membrane. This describes Daelancy's recommended vaginal support levels I, II, and III.[6,7] The floor of the urinary bladder is supported by and near to the front section of the vagina. Between the vagina and the bladder is where the endopelvic fascia is placed. There is no adventitial layer connecting the urethra to the anterior vagina. The ureter travels over the lateral fornix of the vagina. The superior Douglas cavity, the posterior rectum, and the inferior perineal body all serve as boundaries for the posterior vagina (**Figure 1**).[8] The layer that is united with the peritoneum and linked to the posterior surface of the vaginal muscularis is where the rectovaginal septum is an extra layer that develops embryologically. The vagina joins to the cervical ring anteriorly and terminates at the hymenal ring inferiorly.[6]

The tunica mucosa, which is made up of flat stratified epithelium without keratinization, and the lamina propria make up the histological structure of the vagina. The lamina propria, which is located at the base of the epithelium and comprises thick connective tissue rich in elastin fibers, leukocytes, and lymphocytes, as well as many thin papillae that protrude into the epithelial layer, is found there. The tunica adventitia, which lies beneath, is made up of collagen and elastin fibers (**Figure 2**).[8]

The basement membrane divides the vaginal epithelial tissue. A layer of differentiated basal cells sits on top of the basement membrane. There are 5–6 layers of parabasal cells above the basal membrane. Large cells with reticulated nuclei and glycogen vacuoles in their cytoplasm make up the intermediate cell layer. Adult vaginal epithelial cells are typically flat stratified epithelium that undergoes keratinization to produce keratin plates. They also include a tiny amount of keratohyalin. The production of glycogen in vaginal epithelial cells is controlled by estrogen.[8]

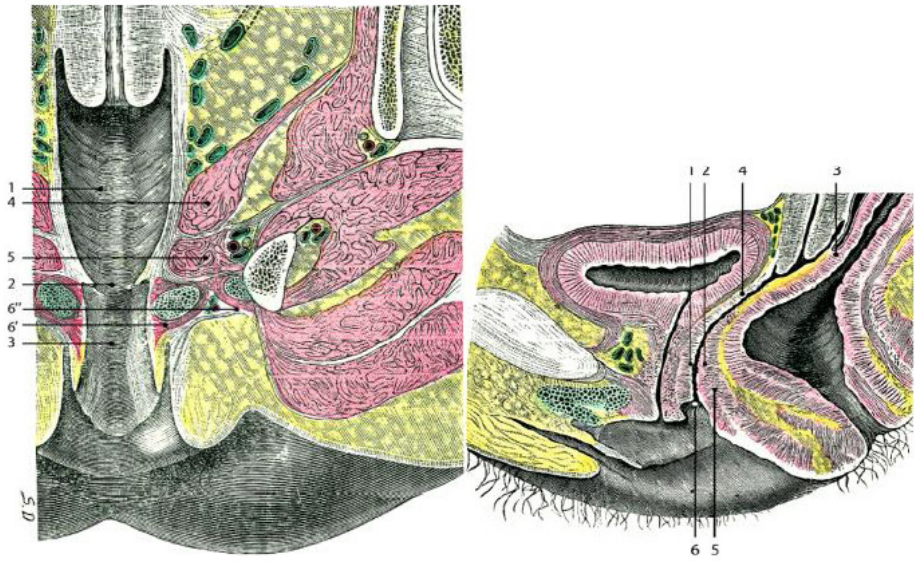

Figure 1. Coronal incision of vagina 1. Subperitoneal vagina; 2. uterine introitus; 3. peritoneal vagina; 4. levator ani muscle; 5. internal transverse muscle; 6'. Bulbospongiosus muscle, 6". Ischiocavernosus muscle (right) Sagittal incision of vagina. 1. anterior vaginal wall; 2. posterior vaginal wall; 3. Douglas base; 4. Vesicovaginal septum; 5. Rectovaginal septum; 6. Vaginal introitus.[8]

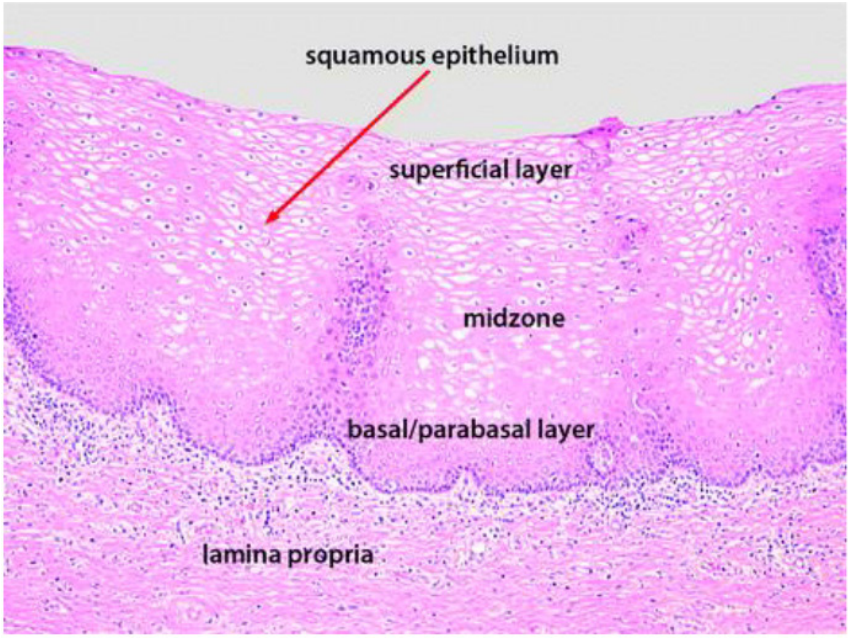

Figure 2. Histology of the vaginal mucosa.[8]

Extracellular matrix

The extracellular matrix (ECM) is a non-cellular structure that regulates almost all of the cellular functions in all human tissues. Normal tissues' homeostasis is a result of tightly controlled interactions between cells and ECM, which preserve a favorable environment for all physiological activities. The major component of the ECM may be thought of as being built from a variety of matrix proteins. These proteins provide cells and tissues the assistance they need. Depending on how they perform, the proteins that make up the ECM can

be classified as either structural or non-structural (also known as glycoproteins). Collagens and elastin are examples of structural proteins, whereas fibronectin, laminin, and tenascin are non-structural proteins. Integrins, growth factors (GFs), and a group of Matrix Metalloproteinases (MMPs) are further significant elements of the ECM.[9]

The main abundant fibrous protein in the extracellular matrix is collagen. Collagens, which make up the majority of the ECM's structural components, control cell adhesion, provide tensile strength, facilitate chemotaxis and migration, and guide tissue growth. Recently, 28 different kinds of collagen have already been described. The other structural protein is elastin, which functions in tandem with collagen. Along with the glycoproteins fibrillin and fibulin, it provides tissue with the ability to recover after continual stretching, such as the dermis of the skin. Its structure is made up of single tropoelastin subunits that are cross-linked with the fibrillin microfibrils on the outside, which are what give elastic fibers their elasticity.[10]

Fibronectin, which is found in the basement membrane (BM) of the ECM and has received less research than collagen, is important for cell adhesion and the body's reaction to injury, wound healing. The ECM has been described as a reservoir for GFs since a number of its elements affect how GFs behave in cell pathways. GFs are activated by a number of processes such as tissue remodeling and wound healing The primary protease enzymes involved in the breakdown of the ECM are known as MMPs. There are currently a large number of MMPs that can deconstruct the matrix. This matrix disintegration is a component of the ongoing ECM remodeling. The ECM of many tissues must go through this crucial transformation process, which, for instance, takes place during neovascularization and tissue remodeling. MMPs are activated as a result of an increase in cytokine and GF activity brought on by tissue healing.[10]

The role of collagen and elastin and fibroblasts in pelvic organ prolapse

The primary fibrillar proteins of connective tissue in the pelvis are collagen and elastin. It is believed that the fibrillar component makes a significant contribution to the biomechanical behavior of tissues (**Figure 3**). Collagen I, III, and V make up the vaginal collagen. The key factors of the vaginal tissue's strength are these three types of collagen. It is well recognized that the overall amount of collagen, the type of collagen, and the degree of collagen cross-linking all have a role in determining the strength of connective tissue.[11,12]

Fibroblasts and other kinds of mesenchymal cells release type III collagen, which makes it crucial in a variety of inflammatory pathologies including lung damage, viral and nonviral liver illnesses, renal fibrosis, hernias, and vascular problems. The interstitial matrix mostly consists of type I collagen and type III collagen. Collagen III promotes tissue flexibility and distension, whereas type I collagen works to offer tissue resistance to tension. This explains why collagen I is mostly found in organized ligaments and structural tissue, whereas collagen III is primarily found in loose tissue, such the areolar membrane.[12]

A protein called elastin helps tissues that often swell and undergo physical stress to remain resilient. Therefore, vascular tissue, lungs, ligaments, bladder, and skin contain the majority of elastin.[13] Elastin aids in the preservation of collagen tissue and the recovery of collagen tissue after deformation (recoil), two biomechanical functions of tissue. Elastin fibers are macromolecular structures that mostly consist of the elastin protein. Early in life, elastin production reaches a peak in the third trimester of fetal life, then steadily diminished during postnatal.[14]

Elastin production in female reproductive organ tissue continues and accelerates, particularly after childbirth. Without requiring energy input, elastin enables tissue to expand and revert to its previous form. This is thought to be crucial in reproductive tissues. This adaptation's special capacity attempts to create fresh elastin fibers that let the vagina expand during pregnancy and then return to normal after delivery.[14] Contrary to collagen's strength, elastin gives tissues flexibility, extension, resilience, and recoil. The quantity of elastin will grow and the amount of collagen will decrease during pregnancy. The role of estrogen itself can increase collagen I expression and increase collagen III degradation in fibroblasts. The strength of the pelvic muscles increases as a result. Additionally, estrogen promotes collagen regeneration and collagen cross-linking.[12]

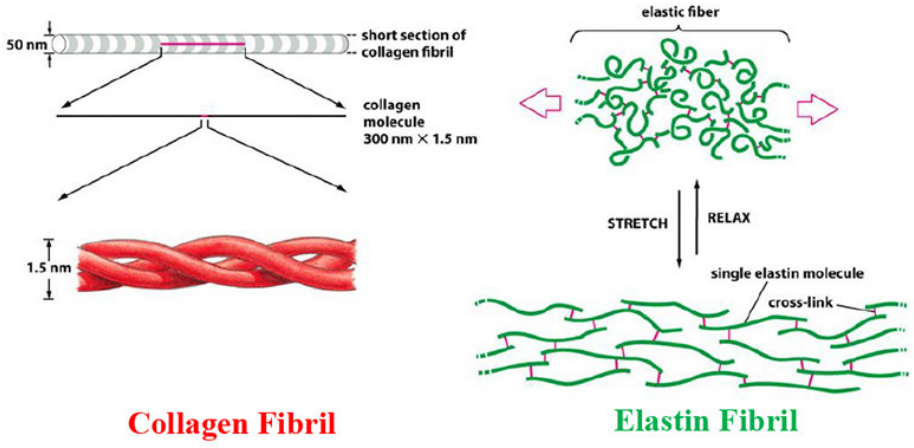

Figure 3. Elastin and collagen fibril.[15]

Matrix Metalloproteinase-9

The processes of tissue remodeling that are pathological and physiological are carried out by matrix metalloproteinases (MMPs). MMPs may handle a variety of non-ECM substrates in addition to cleaving every structural component of the ECM. There are 25 members of this family currently present in vertebrae, 22 of which are found in humans. The fibronectin-like domain of MMP-9 is a special domain that plays a crucial role in the binding of denatured

collagen or gelatin. It is made up of three type II fibronectin repeats that total 58 amino acids. MMP-9 is increased under pathophysiological circumstances during the formation and repair of wounds as well as during diseases involving inflammatory processes, such as cancer, diabetes, and arthritis. The proteolytic characteristics of MMP-9 work in these pathophysiological circumstances to increase the immune response, which starts pathogenesis and accelerates disease development. MMP-9 is increased in cardiovascular diseases, including hypertension, atherosclerosis, and myocardial infarction.[16]

Numerous cell types, including neutrophils, macrophages, and fibroblasts, release MMP-9. MMP-9 is released by a variety of cell types, including neutrophils, macrophages, and fibroblasts, and it plays a significant role in ECM destruction in a wide range of physiological and pathological processes involving tissue remodeling. Stress-related variables such cytokines, growth factors, interleukin (IL)-1, IL-4, IL-6, transforming growth factors (EGF, HGF, TGFB), tumor necrosis factor-alpha (TNF), which regulates MMP transcription, and endocrine are often responsible for controlling MMP activity.[17] Multiple illnesses, including pelvic floor disorders, which have the potential to result in pelvic prolapse, are brought on by disturbances in these factors.

Tissue Inhibitor of Metalloproteinase-1

Tissue inhibitor of Metalloproteinase (TIMP) is an endogenous inhibitor of MMP that also keeps the equilibrium of collagen levels in ECM. Four different TIMPs (TIMP-1, -2, -3, -4) have been identified in vertebrates. TIMP-1 is the variant of the TIMP family that is susceptible to induction and control by substances including phorbol ester, interleukin-1 (IL-1), transforming growth factor (TGF)- 1, retinoids, epithelial growth factor (EGF), interleukin-6 (IL-6), oncostatin, and leukemia inhibitory factor. TIMP-1 expression is suppressed by concanavalin A and dexamethasone.[18]

Typically, TIMP concentrations are higher than MMP concentrations. Different cytokines and growth factors, including plasma protein 2 macroglobulin, surface inhibitors, TGF-ß, TNF-, IL-1, IL-6, and others, control TIMP transcription. TIMP-1's N terminus engages the catalytic domain to prevent MMP activity.[19]

Through processes of synthesis, modification, and destruction, collagen and elastin are kept in equilibrium while undergoing a continuous remodeling process. MMP-9 and TIMP-1 keep the collagen secretion and breakdown processes in equilibrium. According to a number of studies, an imbalance between the processes of synthesis and breakdown results in a less dense extracellular matrix and a sparse yet thick distribution of collagen fibers in women with pelvic organ prolapse.[4,21]

In fibroblasts, estrogen can promote collagen I expression and collagen III breakdown. The strength of the pelvic muscles increases as a result. In addition, estrogen promotes collagen regeneration and collagen cross-linking. Estrogen levels fall and estrogen receptor sensitivity is decreased in menopausal women. Estrogen and estrogen receptors control growth factors in the extracellular matrix. If estrogen levels drop and estrogen receptor sensitivity declines, this weakens the pelvic floor muscles, connective tissue, and ligaments as well as decreases blood flow to the pelvic organs. Because of this, pelvic organ prolapse frequently occurs in menopausal women due to a reduction in the density and contractility of collagen.[11,12]

Vaginal MMP-9 and TIMP-1 Expression

The PCR technique or immunohistochemical imaging can both be used to detect the expression of MMP-9 and TIMP-1. In 2022, Santoso studied a group of women who had uterine prolapse to compare the expression of MMP-9 and TIMP-1 in the uterosacral ligament. Immunohistochemical analysis is used to evaluate its expression. 16 patients from each group had an immunohistochemical analysis. All uterine prolapse patients had vaginal hysterectomies. In contrast to the control group, the uterine prolapse group's median MMP-9 expression was greater, whereas both groups' median TIMP expressions were the same (**Table 1**). A Mann-Whitney test statistical analysis yielded a P-value of 0.004 for the study. It was clear from this that the degree of MMP-9 expression in the two groups varied significantly. When the connection

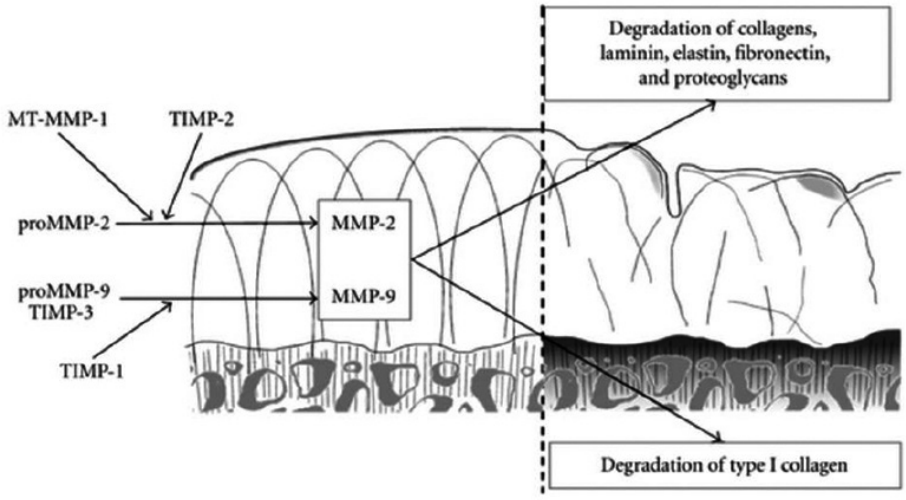

Figure 4. MMP-9 and TIMP-1 on degradation process of collagen.[20]

Table 1. Expression of MMP-9 and TIMP1 in the uterine prolapse and the control groups.[22]

Variable	MMP-9	TIMP-1	r	p-value
Uterine prolapse	6.00 (2-12)	0 (0-2)	0.523	0.02*
Non-uterine prolapse	2.50 (2-12)	0 (0-12)	0.362	0.168*
P-value	0.004*	0.619		
Correlation coefficient r	0.523	0.362		

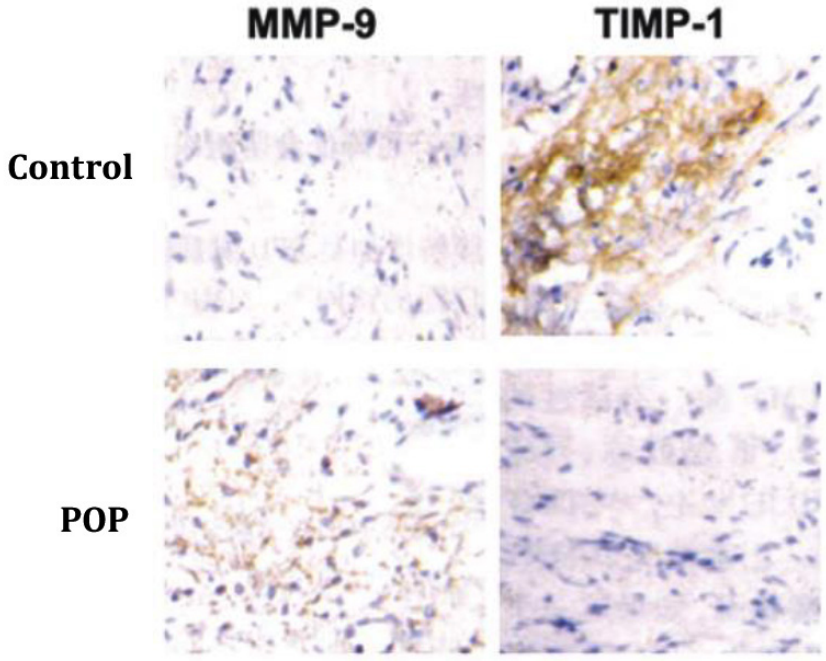

Figure 5. MMP and TIMP-1 expression in the anterior vaginal wall tissues of POP patients and the control: an immunohistochemical investigation.[23]

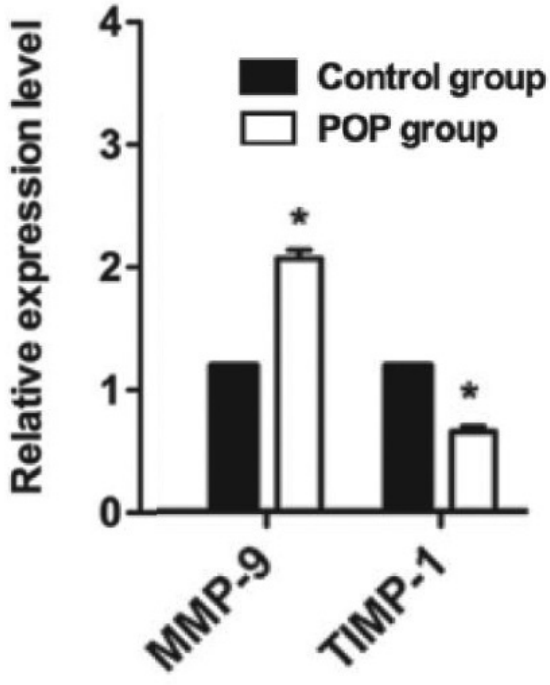

Figure 6. The results of a polymerase chain reaction examination of the expression levels of MMP-9 and TIMP-1 in anterior vaginal wall tissues from POP patients and patients in the control group.[23]

Table 2. Relative expressions of TIMP-1 in the anterior vaginal wall.[24]

	TIMP-1 expressions	
	mRNA	Staining Area
High levels POP	0.3944 ± 0.5420	20.8911 ± 3.7175
Low levels POP	0.5139 ± 0.0480	24.4287 ± 2.0149
Control	0.5401 ± 0.0556	25.6723 ± 1.15634

between MMP-9 and TIMP1 expression was assessed using the Spearman correlation, it revealed a moderate link between the diagnoses. This association was negative (r = -0.523, p = 0.02), which suggests that the MMP-9 score increased with the severity of the uterine prolapse diagnosis.[22]

Another study in 2014 conducted by Wang[23] examined MMP-9 and TIMP-1 in women who experienced and did not experience prolapse. Wang observed the expression of MMP-9 and TIMP-1 by PCR and immunohistochemistry.

All tissue samples of MMP and TIMP showed cytoplasmic positivity, however MMP-9 staining intensities in the POP group were substantially greater than those in the control group (P 0.05). The staining intensity of TIMP-1 was considerably lower in the POP group compared to the control group (p = 0.05), in contrast (**Figure 5**). Wang also did the analysis of the tissue samples' mRNA expression levels using a qPCR test to confirm the immunohistochemical findings. MMP-9 mRNA had substantially increased relative expression levels in the vaginal tissues of the POP group than in the control group (**Figure 6**, p = 0.05 and p = 0.005). As opposed to the control group, the relative expression levels of TIPM-1 mRNA in the POP group were considerably lower (p = 0.05).

Another study carried out by Hu in 2017 similarly yielded finding.[24] Hu evaluated the levels of TIMP-1 on the anterior vaginal wall of the control group and two additional groups with varying POP levels, which are the grade II prolapse group and grade III-IV prolapse group.

The relative mRNA expression of TIMP-1 in high level POP was significantly lower than those in low level POP and the control group (p < 0.05). This can be seen in both mRNA and immunohistochemical examinations (**Table 2**).[24]

CONCLUSION

In summary, the expression levels of MMP-9 were demonstrated to be markedly increased, while TIMP-1 expression levels were decreased in the vaginal wall tissues from POP patients and it is impacted by the level of POP itself as well. The development of uterine prolapse and the

local binding protein are influenced by the differential expression of MMP-9 and TIMP-1, which increases the flexibility of the uterine tissue.

POP is a widespread illness that affects women regularly and has a wide range of risk factors. POP frequently arises via the interaction of several causes rather than just one. This article tells that MMP-9 and TIMP-1 play significant roles in the development of POP through controlling the metabolism of collagen. These findings offer a theoretical framework for investigating POP etiology and creating more potent therapies. Therefore, reducing MMP expression and raising TIMP expression levels may be an efficient strategy to treat POP. These measures may prevent collagen breakdown, raise local collagen levels, and improve tissue elasticity.

DISCLOSURE

Conflict of Interest

The authors report no conflicts of interest in this work.

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Ethics Consideration

This review does not require any form of ethical approval.

Author Contribution

All authors have made the same contribution in searching for journals, analyzing journals, and writing the report on the results of this literature review.

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