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Review article

Collagen changes in pelvic support tissues in women with pelvic organ prolapse

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ABSTRACT

Pelvic organ prolapse is a group of diseases caused by weakened pelvic supportive tissue, but the pathophysiology is not completely understood. Collagen is one of the most important components of the extracellular matrix in connective tissue, as it maintains the supportive functions of the pelvic floor. Collagen I and III are two major subtypes in pelvic tissues. With conflicting results of different studies, changes of their content and ratio are still disputed. The structure of collagen fibrils of pelvic organ prolapse patients become loose, disorderly and discontinuous and become stiffer than control group. Strong mechanical stress and imbalance matrix metalloproteinases /tissue-derived inhibitors of metalloproteinases can lead to collagen anabolism abnormalities causing changes of collagen content and structure. These changes are inter-influenced and are involved by multiple signaling pathways, including TGF-β/Smad, AGE/RAGE, MAPK, PI3K/AKT, and NF-κB. Collagen changes, including content, morphologic and biomechanical changes and catabolism abnormalities, can destroy the supportive function of the pelvic floor and are closely related to the development of pelvic organ prolapse. Epidemiological data also show a genetic predisposition to collagen changes. Research about collagen changes in the pelvic floor supportive tissues is limited and controversial. Small sample sizes and different recruitment criteria, biopsy sites, and research methods make comparisons between various studies difficult. More research concerning collagen changes is needed to better understand the pathogenesis of pelvic organ prolapse.

Contents

Introduction

Pelvic organ prolapse (POP) refers to a group of diseases in which the pelvic organs and adjacent vaginal wall descend due to weakening of the pelvic floor support tissue. POP rarely results in

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serious symptoms or death, but its impacts on the quality of life of patients are enormous and can lead to serious social problems. The incidence of POP is 3–6%, and it can be as high as 50% according to vaginal examination. Approximately 6%–18% of patients undergo surgical treatment. Women aged 60–69 have the highest rate of morbidity [1]. POP is a multifactorial disease with parity, vaginal delivery, age, and BMI as its identified risk factors [2]. POP also has a genetic predisposition, as women with a sibling or maternal history are more likely to develop POP [3].

The organization of pelvic organs into their proper anatomical position relies on a complex system of supportive structures which mainly consist of fascia and ligaments. The supportive function of these structures is mainly dependent on the extracellular matrix (ECM) in connective tissue. The ECM is mostly composed of collagen, elastin, proteoglycans and glycoproteins, of which collagen plays an important role in supportive function [4]. POP sometimes coexists with other diseases, such as joint hypermobility, vertebral hernia, varicose veins, and asthma, as well as some hereditary connective tissue diseases, such as Marfan and Cutis Laxa syndromes [5,6].

Kerkhof MH et al. and De Landsheere L et al. reviewed changes in the ECM and histological changes in the pelvic floor tissue of POP patients in 2009 and 2013 [7,8]. This article will focus on collagen changes and will review recent studies to complement the results of the first two studies. We will further investigate abnormalities of collagen structure, anabolism and metabolism in POP patients and explore the possible causes of collagen abnormalities linked to relevant signaling pathways.

Collagen content

The main collagen subtypes present in the female pelvic floor structures are collagen I and collagen III, while collagen V is present to a lesser degree. Collagen I affects tissue stiffness, and collagen III is related to tissue elasticity, while the role of collagen V is still unknown. Bray et al. showed that the vaginal wall thickness is decreased in women with prolapse. This may be due to reductions in collagen, elastin and smooth muscle [9]. The morphology and content of collagen play an important role in maintaining the pelvic floor support function [4,10].

Since 1996, when Jackson proposed the correlation between POP and collagen content [4], studies on changes in the quantity and ratios of collagen subtypes have yielded inconclusive data. Both increases and reductions in total collagen content in the vaginal wall and pelvic floor supportive tissues have been reported in patients with POP. Some studies have been discussed in previous reviews [7,8]. We also documented the results of some recent studies to complement the two former articles (Table 1).

The most recent studies reported that tissues taken from uterosacral and cardinal ligaments of POP patients had reduced content of collagen I and collagen III [11–14], while opposite results were reported for collagen III by Yucel et al. and Sun et al. [15,16]. Sun et al. also showed that there was no difference in COL1a1 in POP patients compared to the patients in the control group [16]. Analysis of tissue from the vaginal wall showed the same results as Yucel et al. [5,16,17]. Only the study by Kerkhof et al. found that there were no differences in collagen I, III and IV between the POP group and the control group [18].

Some researchers think that collagen content is related to the severity of the prolapse [19]. Kannan et al. and De Landsheere et al. analyzed prolapsed and nonprolapsed tissue derived from the same patient and found no difference in collagen content [20,21].

Primary cultured fibroblasts from uterosacral ligaments, cardinal ligaments and the vaginal wall were also used to examine collagen content changes. Alejandra et al. showed that the percentage of collagen fibers in matrices produced by cells from women with POP was higher than that in cells from controls [22]. Chen et al. reported that the expression levels of procollagens 1A1/1A2/3A1 were significantly lower in the POP group than in the control group [23].

Morphology and biomechanics

Structural changes in collagen fibrils are accompanied by mechanical alterations leading to abnormalities of the biomechanical properties of the pelvic support tissues. Histological changes in pelvic floor tissue showed that collagen fibrils lost their native well-organized, tightly packed morphology and became loose, disorderly and discontinuous structures [13,14]. Using electron

Table 1
Collagen analysis in biopsy specimens from pelvic supportive tissues in patients with POPor without POP.

study	target population and sample size	POP-Q	age	parity	tissue analysed	Analytic methods	Findings: patients with POP compared with controls
Vulic [11]	46 women with POP 49 controls	2-4 0-1	60 (50–70)[a] 59 (51–69)[a]	2 (0–4)[a] 2 (0–5)[a]	left uterosacral ligament	IHC	↓collagen I
Yucel [15]	29 women with POP 35 controls	2-3 0-1	56 (44–72)[a] 54 (43–70)[a]	3(0–11)[a] 3 (0–9)[a]	uterosacral ligament	HE staining, IHC	↓ collagen I and↑ collagen III
Kerkhof [18]	13 women with POP 13 controls	2-3 0	42.9 ± 6.0 44.5 ± 5.0	2.2 (1-3)[b] 2.2 (1-4)[b]	anterior vaginal wall	HE staining, IHC,HPLC	no difference in collagen I and III and IV
HAN [12]	30 women with POP 30 women with POP and SUI 30 controls	– – –	63.24 ± 4.84 63.24 ± 4.84 60.52 ± 6.58	3.75 ± 0.68 3.75 ± 0.68 1.83 ± 0.92	cardinal ligaments, uterosacral ligaments and paraurethral tissues	HE staining and Masson's trichrome staining	↓ collagen I and III
Vetuschi [5]	14 women with POP 10 controls	3 0	55 55	– –	anterior vaginal wall	HE staining, Masson's trichrome and Weigert-van Gieson stain, IHC, IF	↓ collagen I and↑ collagen III
Sun [16]	22 women with POP 34 controls	2-3 0	45.7 ± 4.3 44.9 ± 4.1	3.1 ± 1.0 2.6 ± 1.0	uterosacral ligament	qPCR IHC	no difference in COL1a1 and↑COL3a1
Liu [13]	30 women with POP 30 controls	2-4 0-1	58.6 ± 4.1 57.1 ± 3.3	– –	uterosacral ligament	Masson's trichrome staining, IHC, qPCR	↓ collagen I and III
Zeng [14]	50women with POP 50 controls	2-4 0	60.8 ± 6.9 57.1 ± 5.5	3.4 ± 0.8 3.0 ± 0.7	uterosacral ligament and anterior vaginal wall	HE staining, IHC, WB	↓collagen I and III
Vetuschi [17]	20 women with POP 10 controls	3-4	57 ± 14	– –	anterior vaginal wall	HE, Masson Trichrome and Van Gieson staining, IHC	↓ collagen I and↑ collagen III

IHC: Immunohistochemistry. HE staining: Hematoxylin-eosin staining. HPLC: High-performance liquid chromatography. qPCR: Quantitative polymerase chain reaction. WB: Western blotting. IF: Immunofluorescence.
[a] Mean (range).
[b] median (interquartile range).

microscopy, some researchers observed that collagen fibrils lost their normal parallel structures in the affected vaginal tissue and formed a sparsely “whorled" pattern. The diameter of collagen fibrils was thicker than normal and had large gaps [12,24–26]. Kim et al. used atomic force microscopy (AFM) to observe collagen fibrils in the pelvic floor tissues of POP patients and found that they were wider, thicker, more uneven and flatter with some stunted ends and had a reduced D-period. Collagen fibrils formed by single fibrils were absent from braided bundles [10].

The vaginal wall tissue of POP patients is significantly stiffer than that of the patients in control group [27]. ECM secreted by fibroblasts extracted from the uterosacral ligaments of POP patients is also stiffer than that from patients in the control group [22]. Some studies confirmed that the ratio of collagen subtypes in the pelvic support tissue of POP patients changed, with relative increases in collagen I and decreases in collagen III [10,25]. Kim et al. generated models of collagen matrices with different ratios of collagen subtypes to identify possible reasons for changes in the mechanical properties of the pelvic support tissue and found that the stiffness increased as the ratio of collagen I/III increased; however, the stiffness was still far different from that of the POP group [10], suggesting that the pathophysiology of POP cannot be explained only by changes in the ratio of collagen subtypes.

Mechanical stimulation can also affect ECM secretion. Strong mechanical stress can upregulate MMP expression and down-regulate collagen expression through the PI3K/AKT and TGF-β/Smad pathways and can affect cell adhesion [13,28–31].

Collagen catabolism

The ECM in pelvic floor tissues is kept in balance by the opposing effects of decomposition and synthesis, and its stability mainly depends on the balance of matrix metalloproteinases (MMPs), which are secreted by fibroblasts, and their inhibitory factors, tissue-derived inhibitors of metalloproteinases (TIMPs). Based on substrate preference and domain organization, MMPs are grouped into different subtypes. Collagenases, including MMP-1, MMP-8 and MMP-13, cleave interstitial collagens I, II and III into characteristic 3/4 and 1/4 fragments, while MMP-2 and MMP-9 are gelatinases, which can digest those fragments into amino acids [32,33]. An appropriate ratio of MMPs and TIMPs can stabilize the amount of collagen in the ECM and thereby maintain the structure of the pelvic floor support tissue.

Many studies have analyzed changes in MMPs and TIMPs in the pelvic floor connective tissue of patients with and without POP using various methods. Some of the findings published before 2011 have been listed in the review by Kerkhof et al. [7] and the study by Sun et al. [16]. In most studies, POP patient tissue shows an upward trend in MMPs and a downward trend or no change in TIMPs. Recent studies also indicated that MMPs were upregulated in POP patient tissue; however, the expression changes for TIMP remain controversial [5,13,17,34] (Table 2).

Fibulin-5 can inhibit the activity of MMP-9, and a decrease in fibulin-5 and an increase in MMP-9 have been detected in the vaginal wall of POP patients [35]. Puerarin can enhance the expression levels of TIMP1 and inhibit MMP-2 and -9 expression [36].These factors provide novel approaches for the treatment of POP [36,37].

Signaling pathways

AGE/RAGE

In 1996, Jackson et al. first proposed that collagen fibers in the pelvic floor are easily broken and that the new collagen is unable to exert its normal mechanical functions due to the increase in AGEs in the connective tissue [4]. Jackson et al. verified his hypothesis in 2002 [38]. In recent studies, Chen et al. and Vetuschi et al. also found that the expression of AGE in vaginal tissues was increased in patients with POP, whereas RAGE was not different [17,39].

TGF-β/Smad

TGF-β is a key inflammatory factor in injury repair and is involved in the synthesis of ECM, the differentiation of fibroblasts into myofibroblasts, the inhibition of MMP and the promotion of TIMP expression. TGFβ1 and smad7 were reduced and Smad2,3 and p-Smad3 were increased in tissue from POP patients [13,17]. Moreover, increased mechanical strain can reduce the expression of TGFβ1 [28,29].

In addition, the MAPK, PI3K/AKT, and NF-κB pathways are also involved in the development of POP and are known to cross-talk with the AGE/RAGE and TGF-β/smad pathways [17,39–41].

Heredity

Studies showed that the risk of prolapse in siblings of women with severe prolapse was increased by 5 times compared to the general population [42]. A study of large samples of twins also pointed out that genetic and nonshared environmental factors similarly contributed to approximately 40% of the variation in the likelihood of developing POP [43]. So far, there are three major types of research of POP genetic epidemiology: genome-wide association studies, linkage analyses and candidate gene association studies. The main candidate genes include collagen type 1 alpha 1 (COL1A1), collagen type 3 alpha 1 (COL3A1), laminin

Table 2
Analysis of MMPs and TIMPs in pelvic supportive tissues in patients with POP and without POP.

study	target population and sample size	POP-Q	age	parity	tissue analyzed	Analytic methods	Findings: patients with POP compared with controls
Alarab [50]	17 women with POP 19 controls	3-4 0	43 ± 8 46.4 ± 8	2.81 (1,4)[a] 1.8 (0,3)[a]	anterior vaginal wall	WB, qPCR, Luminex Assay, Zymography, IHC	↑MMP2 and↓TIMP1 No difference in MMP1/9/12,TIMP2/3/4
Wang [51]	72 women with POP 72 controls	2-3 0-1	59.01 ± 7.657 59.53 ± 8.962	2.24 ± 0.617 2.29 ± 0.615	anterior vaginal wall	IHC, qPCR	↑ MMP1/2/3/9 and↓TIMP1
Leegant [52]	21 women with POP 19 controls	2-4 0	59.6 ± 9.6 46.1 ± 9.6	3(0-11)[a] 2(0-4)[a]	uterosacral ligaments	IHC	no difference in MMP9
Vetuschi [5]	14 women with POP 10 controls	3 –	55 ± 5.38 55 ± 5.38	– –	anterior vaginal wall	IHC	↑MMP3 and↑ TIMP1
Liu [13]	30 women with POP 30controls	2-4 0-I	58.6 ± 4.1 57.1 ± 3.3	2.3 ± 1.6 2.4 ± 1.1	uterosacral ligament	IHC, qPCR	↑MMP2/9 and↓ TIMP2
Vetuschi [17]	20 women with POP 10 controls	3-4	57 ± 14 57 ± 14	– –	anterior vaginal wall	IHC	↑MMP3 and ↑TIMP1

IHC: Immunohistochemistry. qPCR: Quantitative polymerase chain reaction. WB: Western blotting.
[a] Mean(range).

gamma-1 (LAMC1), matrix metalloproteinase 9 (MMP-9), matrix metalloproteinases 1 and 3 (MMP-1 and -3), lysyl oxidase-like 1 (LOXL1), estrogen receptor alpha (ERa), estrogen receptor beta (ERb) and progesterone receptor (PGR) [44,45]. Ward et al. performed a systematic review and demonstrated that in contrast to the GG genotype, the COL3A1 rs1800255 AA genotype is correlated with POP in Asian and Dutch women [44]. Another systematic review and meta-analysis showed that the rs1800012 polymorphism of the COL1A1 gene was associated with prolapse occurrence [45].

Limitations and future research

POP is a multifactorial disease common in older women and is currently considered a disorder of pelvic floor dysfunction caused by the degenerative weakening of pelvic supportive structures. Both environmental and genetic factors can lead to relaxation of the pelvic floor tissue, which changes the histological and mechanical properties of the pelvic floor and eventually leads to POP. Based on previous studies, collagen, as an essential component of connective tissue, is the main contributor to the maintenance of resistance ability in the pelvic floor support structures. However, the use of different evaluation methods and sample tissue sites makes comparison between studies difficult.

Most of the studies were based on optical microscopic observation of tissues by chemical staining, including hematoxylin and eosin, picrosirius, Masson's trichrome, Gomori's trichrome and Verhoeff elastic stains. There are differences in pressure loads at different prolapse sites, so use of different biopsy sites and different histological observation locations can lead to bias. Pathological diagnosis is influenced by the subjective judgment of the pathologist. PCR is an objective method for detecting changes in collagen, but collagen consists of three α chains. PCR also can only be performed on a single α chain.

Differences in patient recruitment for POP cases and non-POP cases also make the horizontal comparison between studies difficult. Most studies described the age of patients but did not report the age of onset and duration of POP. Some studies chose patients with 2° of prolapse or more as the experimental group and used patients with 0–1° of prolapse as the control group. Although degree 1 prolapse is often considered a change associated with normal aging of the vagina [46], some patients are too young to develop more severe prolapse and are considered part of the control group. Therefore, strict gynecological examinations and demographic statistics should be reported for each case.

Delivery is an important risk factor for POP. The pelvic floor tissue suffers a great tensile force during the delivery process and damages the pelvic floor support tissue. Many studies verified that mechanical stretching had an impact on ECM in the pelvic floor [13,28]. Intrinsic changes in the ECM due to genetic factors can affect the mechanical endurance of the pelvic floor tissue [44,45]. Therefore, it is still unclear whether ECM changes are the cause or consequence of POP. Consistent with the observed histologic changes, studies on genetic factors mostly involved collagen and MMPs; however, specific mutations or susceptibility genes have not been determined. Further studies on the genetic factors of POP are needed to better understand the pathogenesis and risks of POP. This genetic knowledge will inform surgeons' choice of mesh or native tissue in prolapse surgery and high-risk women's choice to use exercise as a preventative measure against POP.

Collagen maintenance is controlled by a series of signaling pathways, including the TGF-β/Smad, PI3K/AKT, MAPK, NF-κB, and AGE/RAGE pathways, and there is cross-talk between each pathway that regulates collagen metabolism [41,47–49]. However, few pathways have been studied in the context of POP pathogenesis, and a deep mechanistic understanding is lacking.

Conclusion

Collagen changes of content, structure, biomechanics and catabolism lead to pelvic supportive tissue of POP women weakening causing the process of POP. However, the current knowledge of changes and their mechanisms in pelvic floor collagen of women with POP is limited and controversial. Small sample sizes and different recruitment criteria, biopsy sites, and research methods make comparisons between various studies difficult. It is still unclear whether the changes in collagen are a cause or an effect of POP. Researchers need to innovate, optimize and standardize research conditions and continue studies to clarify the mechanisms underlying the development of POP.

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