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Sottner O[1], Halaska M[1], Gabriel B[2], Benkova K[3], Maxova K[1], Zahumensky J[1], Kolarik D[1], Hurt K[1], Gitsch G[2], Kittnar O[4]
1. *Department of OB/Gyn, University Hospital Na Bulovce, 1st Faculty of Medicine, Charles University in Prague, Czech Republic,* ***2.*** *Department of OB/Gyn, Freiburg University Medical Centre, University of Freiburg, Freiburg, Germany,* ***3.*** *Department of Pathology, University Hospital Na Bulovce, Prague, Czech Republic,* ***4.*** *Department of Physiology, 1st Faculty of Medicine, Charles University in Prague, Czech Republic*

ALTERATIONS IN EXTRACELLULAR MATRIX PROTEINS OF THE UTEROSACRAL LIGAMENTS IN WOMEN SUFFERING FROM PELVIC ORGAN PROLAPSE

Hypothesis / aims of study

The aim of this study is to describe and compare the expression of extracellular matrix proteins in the uterosacral ligaments of women with and without pelvic organ prolapse in order to clarify its pathogenesis.

Recent studies indicate that pelvic organ prolapse can, at least in part, be defined as a connective tissue disease. High rates of pelvic organ prolapse and urinary incontinence were found in patients suffering from connective tissue disorders (e.g. Marfan syndrome and Ehlers-Danlos syndrome) and there is some evidence that abnormalities of the connective tissue composition may contribute to the genesis of pelvic organ prolapse in all patients. (1, 2) The uterosacral ligaments are an important part of the pelvic support system and establish the level 1 support of the cervix and the upper vagina. As such the extracellular matrix composition of the uterosacral ligaments could play an important role in pathogenesis of the uterine prolapse.

Study design, materials and methods

We investigated the set of 117 women who underwent hysterectomy. The first group consisted of 78 women operated for pelvic organ prolapse - POP group. These females suffered from pelvic organ prolapse, as defined by the descent of the cervix to, or beyond, the introitus (ICS POP-Q point C was “0” or more). The second group comprised of 39 control females with no pelvic organ descent (ICS POP-Q stage 0) but suffering from any other benign disease of a genital tract (e.g. menorrhagia) – non POP group. Pelvic malignancies were excluded. Biopsies of the right and left uterosacral ligaments were obtained during hysterectomy. The biopsies were performed at the level of the cervical insertion of the uterosacral ligament using a standardized technique. All biopsy specimens were fixed in formalin and embedded in paraffin. The standardized immunohistochemical protocols were used. A panel of extracellular matrix proteins was evaluated by immunohistochemistry. Monoclonal antibodies against collagen I, II, III, IV, V, VI and against MMP-1, MMP-2, MMP-9, MMP 13 (Medicorp Inc., Canada); monoclonal antibody against laminin (Dako, Denmark) and polyclonal antibody against fibronectin (Dako, Denmark) were used. All slides were separately examined by two experienced pathologists blinded to the clinical diagnosis. Minimal or no staining reaction was scored as (-), a weak reaction was scored as (+) and a strongly positive staining reaction was scored as (++). The data were analyzed and the groups were compared. For statistical analysis, the exact Fisher test and chi square test were used.

Results

The left and right uterosacral ligaments of 117 women were analyzed. Concerning the demographic parameters, the only significant difference was in mean age: POP group 65 years and non POP group 52 years of age. There was no difference in parity, menopausal status and use of hormonal replacement therapy. We found a significantly higher expression of collagen I ($p=0,016$), collagen IV ($p=0,020$) and collagen V ($p=0,029$) in the POP group. There was no difference in collagen III and collagen VI expressions - both groups showed similarly high patterns. Collagen II was expectantly not found in any of samples. We were also not able to prove a higher expression of fibronectin in POP patients. The laminin expression was low in both groups. Nevertheless, it was even lower in the pelvic organ prolapse group where all samples but nine expressed no laminin but the statistically significant level was not reached. The expressions of matrix metalloproteinases were remarkably lower in POP group – mainly MMP-2 ($p=0,016$) and MMP-13 ($p<0,001$) showed noticeably lower expression in pelvic organ prolapse sufferers; MMP-1 and MMP-9 indicated the same trend but the statistically significant level was not reached.

Interpretation of results

The uterosacral ligaments of women suffering from pelvic organ prolapse show significantly higher collagen I, IV and V expressions compared to the control women. The expressions of collagen III, collagen VI and fibronectin are constantly high irrespective of pelvic organ prolapse. Generally low laminin expression was even lower in the pelvic organ prolapse group. Importantly, we demonstrated a remarkably lower appearance of matrix metalloproteinases in uterosacral ligaments of pelvic organ prolapse sufferers which can indicate alterations in metabolism of extracellular matrix.

Concluding message

To conclude, we consider the evidence of reduced MMP activity and change in expression of nucleator collagen subtype (collagen V) as important in the search of pathogenesis of the pelvic organ prolapsed (3). We continue in this project to be able to state more substantiated results and to contribute more to the evidence on connective tissue alterations in pathogenesis of the pelvic organ prolapse.

References

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Is this a clinical trial?	**No**
What were the subjects in the study?	**HUMAN**
Was this study approved by an ethics committee?	**Yes**
Specify Name of Ethics Committee	**Local Ethics Committee of the University Hospital Na Bulovce, Prague, Czech Republic.**
Was the Declaration of Helsinki followed?	**Yes**
Was informed consent obtained from the patients?	**Yes**