



**Karolinska
Institutet**

Department of Woman and Child Health

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STUDIES ON THE EXTRACELLULAR MATRIX OF THE DYSFUNCTIONAL PELVIC FLOOR

AKADEMISK AVHANDLING

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Abstract

Objective: Pelvic floor dysfunction cause impaired quality of life of many women and is one of the most common reasons for gynaecological surgery on benign indications. Little is known about the pelvic floor extracellular matrix as a pre-requisite for mechanical sustainability through vaginal delivery, age and hormonal changes. For this reason, pelvic floor extracellular matrix was investigated in women suffering from the two major dysfunctional conditions, pelvic organ prolapse (POP) and stress urinary incontinence (SUI), regarding molecules responsible for tensile strength and elasticity.

Methods: Para-urethral biopsies were collected from women with POP, SUI and compared to matched healthy controls according to menopausal status or age. The collagen concentration and extractability by pepsin digestion were analyzed in women with POP. Real-time RT-PCR revealed the gene signals and immunohistochemistry the protein expressions of collagen I, collagen III, the small leucine-rich proteoglycans (SLRPs) decorin, lumican and fibromodulin as well as the elastin associated proteins fibrillin-1 and fibulin-5 in POP and SUI. In SUI the sex steroid hormone receptor isoforms and subtypes ER- α , ER- β , PR-(A+B), PR-B and AR were identified and quantified by scoring and image analysis (ER- α and ER- β) completed by mRNA expressions analyze of ER- α , ER- β , PR and AR by real-time RT-PCR.

Results: The collagen concentration was 30 % lower in the pelvic floor ECM of women younger than 53 years suffering from POP. There were lower mRNA expressions of all the investigated SLRPs and the elastin associated fibulin-5 in pre-menopausal women with POP. A 16-fold reduction of decorin mRNA was most prominent with a corresponding weaker protein expression of decorin. Postmenopausal women with POP exposed significantly lower mRNA expressions of fibromodulin and fibulin-5. A significant reduction of the mRNA expression of fibrillin-1 seen in women with SUI irrespective of menopausal status was confirmed by a lower immunoreactivity. All hormone receptor isoforms or subtypes were expressed in the pelvic floor ECM with ER- β showing an increased expression in pre-menopausal women with SUI. A corresponding elevation in gene expression was not discovered.

Conclusion: Evidence for POP and SUI deriving from different alterations in the pelvic floor ECM has been found. The results therefore suggest different pathophysiological backgrounds to these conditions on the tissue level. Furthermore are the greatest changes found in the pre-menopausal POP, reflecting the severity of pelvic floor dysfunction in this group. All investigated hormone receptor isoforms or subtypes were expressed. The ER- β protein was more expressed by in pre-menopausal women with SUI.

Key words: *Pelvic floor, pelvic organ prolapse, stress urinary incontinence, extracellular matrix, collagen, SLRPs, decorin, lumican, fibromodulin, elastin associated proteins, fibrillin-1, fibulin-5, sex steroid hormone receptors, ER, PR, AR*