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Deciphering the interplay between NEAT1, miR-139-5p, miR-129-5p, TGF-β1, and collagen type I in pelvic organ prolapse

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ABSTRACT

Objective: Pelvic organ prolapse (POP) is a benign gynecological disorder characterized by the descent of pelvic organs due to weakened support structures. While the molecular mechanisms behind POP are not fully understood, previous studies have indicated an association with altered levels of collagen type I and transforming growth factor-beta 1 (TGF-β1). Long non-coding RNAs (lncRNAs) and microRNAs (miRNAs), which are essential regulators of gene expression, may provide valuable insights into the diagnosis, prognosis, and treatment of POP. This study aimed to investigate the protein levels of TGF-β1 and collagen type I, as well as the expression levels of miR-129-5p, NEAT1, and miR-139-5p key regulators of TGF-β1 and collagen type I among patients with POP.

Materials and Methods: Thirty-four POP patients and thirty healthy controls were included in the study. The expression levels of miR-129-5p, NEAT1, and miR-139-5p were measured using quantitative polymerase chain reaction on RNA extracted from fascia tissues. TGF-β1 and collagen type I protein levels were assessed via ELISA.

Results: Compared to healthy controls, POP patients exhibited significantly higher levels of miR-129-5p (p=0.011) and TGF-β1 (p=0.000).

Conclusion: The findings suggest that miR-129-5p may play a crucial role in the pathophysiology of POP. Future studies should explore the role of lncRNAs in regulating miR-129-5p and their potential relationship with POP.

Keywords: miRNA; lncRNA; TGF-β1; pelvic organ prolapse; collagen

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INTRODUCTION

Pelvic organ prolapse (POP) is a disorder of pelvic floor dysfunction characterized by loss of pelvic wall uterine herniation, support and vaginal prolapse. Although some conditions and molecules are considered to be effective in the etiology of POP, the disease is known to be multifactorial.[1] Anatomical, physiologic, genetic, lifestyle and reproductive factors such as chronic cough, constipation, hysterectomy, childbirth and heavy lifting influence the development of POP, with a constant increase in intra-abdominal pressure.[2]

POP disease has shown multiple risk factors contribute to the degradation of pelvic floor connective tissue and collagen, resulting in damage to muscles, connective tissue, blood vessels, and nerves.[3] In 1996, Jackson established a link between POP and collagen content. Since then, several studies have shown varying results, with some reporting an increase and others a decrease in the total collagen content of the vaginal wall and pelvic floor support tissues in POP patients.[4] Transforming growth factor-beta 1 (TGF-β1), which remodels the extracellular matrix (ECM) by regulating numerous enzymes and ECM components, stimulates collagen expression. Studies have determinate that TGF-β1 expression level decreased in different tissues from women diagnosed with POP.[5]

The mammalian genome contains sequences for both protein-coding RNA and non-coding RNAs (ncRNAs). There are many different groupings of known ncRNAs. In particular, ncRNAs longer than 200 nucleotides are called lncRNA and are involved in different biological and molecular processes. Involved in many steps of gene regulation, lncRNAs, especially micro RNA (*miRNA/miR*), regulate gene expression before and after transcription. miRNAs, which are approximately 21-25 nucleotides long, bind to mRNAs and cause their degradation or suppression of translation. Studies have shown that ncRNAs have crucial roles in the emergence and development of different diseases.[6,7]

The association of miR-129-5p, NEAT1 and miR-139-5p with POP disease has not been previously shown in the literature. The aim of our study was to elucidate the association of miR-129-5p, NEAT1 and miR-139-5p, which are known to be effective in TGF-β1 and collagen type I regulation, with POP disease. The primary goal of our study is to present new biomarker targets that will contribute to the diagnosis and treatment of POP disease and fill the research deficiency in the literature.

MATERIALS AND METHODS

Collection of Sample Material

The study was approved by the Clinical Research Ethics Committee of Muğla Sıtkı Koçman University (approval number: 19/II, date: 15.09.2021). A total of 64 participants were enrolled, including 34 patients diagnosed with POP who received surgical treatment, and 30 control individuals who underwent hysterectomy without a POP diagnosis. All participants were recruited from the outpatient Clinic of the Department of Obstetrics and Gynecology, Muğla Sıtkı Koçman University Faculty of Medicine. Informed consent was obtained from all participants prior to their inclusion in the study.

Two 0.5x0.5 cm pieces of tissue were removed from the patients' pubocervicovaginal fascia (PSVF) during the surgical procedure. Two pieces of 0.5x0.5 cm tissue were removed from the PSVF of patients who had benign hysterectomy procedures but did not have POP as a control group. The tissues were kept at -80 °C in RNA later solution.

Gene Expression Analysis

Total RNA was extracted from tissue samples using the total RNA extraction Kit (MG-RNA-01-250, Hibrigen), with 50 mg of tissue processed for each sample. The levels of miR-129-5p expression, NEAT1, and miR-139-5p were determinate by using the SYBR green real time-quantitative polymerase chain reaction (RT-qPCR) technique. RNA extracted from the tissue samples was first transcribed into complementary DNA (cDNA) using the cDNA synthesis kit (A.B.T.™, C03-01-20). The resulting cDNA was then analyzed with the 2X SYBR Green qPCR Mix (Hibrigen, MG-SYBR-01-80) and specific primers (Table 1) to determine the expression levels of the target genes. In this study, miR-26a served as the reference gene for miR-139-5p and miR-129-5p, while GAPDH was used as the reference for NEAT1.[8,9] The relative gene expression levels were assessed using the $2^{-\Delta\Delta CT}$ method, with data derived from no fewer than three independent experiments.

Enzyme-Linked Immunosorbent Assay (ELISA) Anaysis

For each sample, 50 mg of tissue was homogenized in 80 µL of cold PBS using a tissue homogenizer. Quantification of TGF-β1 and collagen type I levels was performed using the Human TGF-β1 ELISA Kit (SunRedBio, Cat. No: 201-12-0135) and the Human COL-1 ELISA Kit (SunRedBio, Cat. No: 201-12-2078), following the manufacturer's protocols. The results were expressed in ng/mL.

Statistical Analysis

Statistical analyses were performed using SPSS version 22 for Windows (SPSS Inc., Chicago, IL, USA). Normality of gene expression data was assessed using the Shapiro-Wilk test. Independent t-tests were applied to normally distributed data, while the Mann-Whitney U test was used for non-normally

Table 1. Primers sequences	
Gene/ncRNA	**Primers**
NEAT1	**F** 5' ATGCCACAACGCAGATTGAT 3' **R** 5' CGAGAAACGCACAAGAAGG 3'
miR-139-5p	**F** 5'ACACTCCAGCTGGGTGTAGTGTTTCCTACTT 3' **R** 5'CTCAACTGGTGTCGTGGAGTCGGCAATTCAGTTGAGCTGGAGAC 3'
miR-129-5p	**F** 5' ACACTCCAGCTGGGCTTTTTGCGGTCTGG 3' **R** 5'CTCAACTGGTGTCGTGGAGTCGGCAATTCAGTTGAGGCAAGCCC 3'
miR-26a	**F** 5'ACACTCCAGCTGGGTTCAAGTAATCCAGGA3' **R** 5'CTCAACTGGTGTCGTGGAGTCGGCAATTCAGTTGAGAGCCTATC3'
GAPDH	**F** 5' GAAGGTGAAGGTCGGAGTC 3' **R** 5'GAAGATGGTGATGGGATTTC 3'

distributed data. Descriptive statistical data are presented as minimum, maximum, and mean ± standard deviation. A *p*-value of <0.05 was considered statistically significant.

In silico Analysis

To confirm our experimental findings, we identified and analyzed the target genes of miR-129-5p whose expression was significantly changed. The target genes of miR-129-5p were identified using the miRDB (https://mirdb.org/mirdb/index.html) tool. Gene ontology (GO) analysis was obtained using target mRNA matches with target scores of 95% and above. Target genes of miR-129-5p were analyzed using GO and pathway analyses using GeneCodis4 (https://genecodis.genyo.es/).[10]

RESULTS

Evaluation of miR-129-5p, NEAT1 and miR-139-5p Expression Levels

In the study, miR-129-5p, NEAT1 and miR-139-5p expression distributions were analyzed by RT-qPCR and $2^{-\Delta\Delta CT}$ mean and *p*-values were examined in patients with POP and control groups without POP diagnosis (Table 2).

When miR-129-5p expression level was analyzed in POP patients compared to control groups, a significant increase was detected in the patient group (p=0.011) (Figure 1). However, no significant difference was observed in miR-139-5p and NEAT1 expression levels between the two groups (p=0.492 and p=0.570, respectively).

Evaluation of Collagen Type I and TGF-β1 Protein Levels

In our study, collagen type I and TGF-β1 protein levels were analyzed using ELISA method and mean protein levels and *p*-values were examined in patients with POP and control groups without POP diagnosis (Table 3).

Comparison between POP and control groups revealed a significant difference in TGF-β1 level (p=0.000) (Figure 2), while no significant change was observed in collagen type I level (p=0.091).

In silico Analysis

miR-129-5p, which we determined to be effective in the mechanism of POP, was analyzed with the miRDB tool and 70 genes with a target score of 95% and above were identified. As a result of the examination with the GeneCodis 4 web tool, the common molecular functions, cellular components, biological processes and pathway analysis (KEGG pathway) in which the 70 identified genes are involved are shown in Figure 3.

DISCUSSION

Investigating the pathophysiology of POP disease and aiming to contribute to the existing literature, our study delved into the influence of NEAT1 on miR-129-5p and miR-139-5p, along with exploring the relationship between miR-139-5p and TGF-β1, and miR-129-5p and collagen type I in POP. Expression and protein

Table 2. miR-129-5p, NEAT1 and miR-139-5p expression levels in POP and control groups			
ncRNAs	**POP (mean ± SD)**	**Controls (mean ± SD)**	***p****
NEAT1	1.15±1.09	0.85±0.51	0.492
miR-139-5p	35.72±28.81	44.59±40.08	0.570
miR-129-5p	6.80±6.63	3.48±5.46	**0.011**
*: Mann-Whitney U test, SD: Standard deviation, POP: Pelvic organ prolapse, lncRNAs: Non-coding RNAs			

level results were meticulously assessed through statistical analysis. Comparative analysis of miR-129-5p, NEAT1 and miR-139-5p expression levels unveiled a significant elevation in miR-129-5p expression among POP patients in contrast to controls (p=0.011). Conversely, no substantial discrepancies were observed in NEAT1 and miR-139-5p expression levels (p=0.492 and p=0.570, respectively). Notably, scrutiny of TGF-β1 and collagen type I protein levels revealed a marked increase in TGF-β1 protein levels in POP patients relative to controls (p=0.000), while collagen type I levels exhibited no significant difference (p=0.091). Utilizing the miRDB tool, we identified target mRNA matches of miR-129-5p, deemed pivotal in POP mechanisms, with target scores exceeding 95%. To further unravel the pathogenesis of POP disease, GO and pathway analyses were conducted on these target mRNAs, leading to the identification of novel targets priming future investigations.

POP is a gynecological condition defined by the descent of one or more pelvic organs such as the small intestine, uterus, bladder, vagina, or rectum from their normal anatomical positions due to weakened supporting structures.[11] The pathophysiology of POP encompasses a spectrum of molecular mechanisms, yet its complexity remains incompletely elucidated. Notably, connective tissue impairment and consequent weakening emerge as pivotal contributors to POP development.[12] Constituting a fundamental human tissue, connective tissue comprises fibrous ECM components. Perturbations in ECM structure and composition are widely recognized as correlates of connective tissue pathologies. Among the ECM's protein constituents, collagen and elastin assume central roles in dictating its mechanical properties.[13]

In mammalian systems, the potential involvement of TGF-β1 in physiological tissue repair and collagen deposition has been substantiated through empirical investigations. Specifically, research has established its role in fostering the synthesis of collagen and fibronectin via transcriptional activation mechanisms.[14] Given its implication in numerous pathological conditions, TGF-β1 has been extensively scrutinized in endeavors to decipher the molecular underpinnings of POP. Qi et al.,[15] in their investigation, documented a diminished expression of TGF-β1 protein within the POP cohort relative to the control group, shedding light on its potential relevance in the pathogenesis of POP.

In the exploration of uterine prolapse, Li et al.[16] uncovered an inverse relationship between TGF-β1 expression and the progressive severity of the condition. Conversely, investigations into POP conducted in Türkiye yielded contrasting findings, indicating no significant alterations in TGF-β1 levels across studied groups in serum samples.[17] Examining postmenopausal cohorts with and without POP, comparable TGF-β1 expression

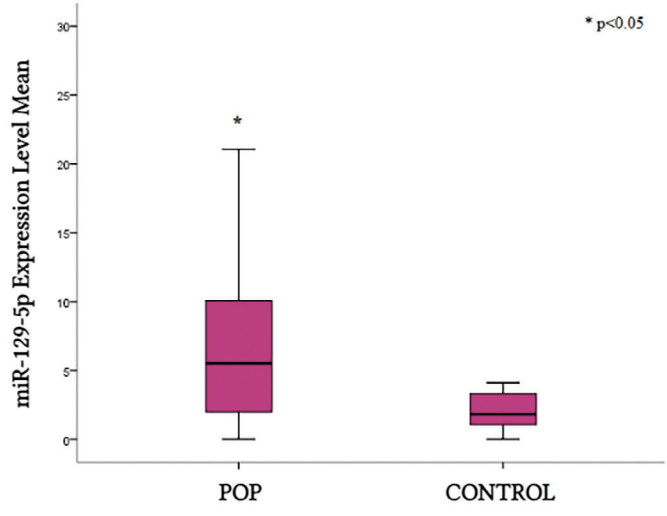

Figure 1. miR-129-5p expression level

POP: Pelvic organ prolapse

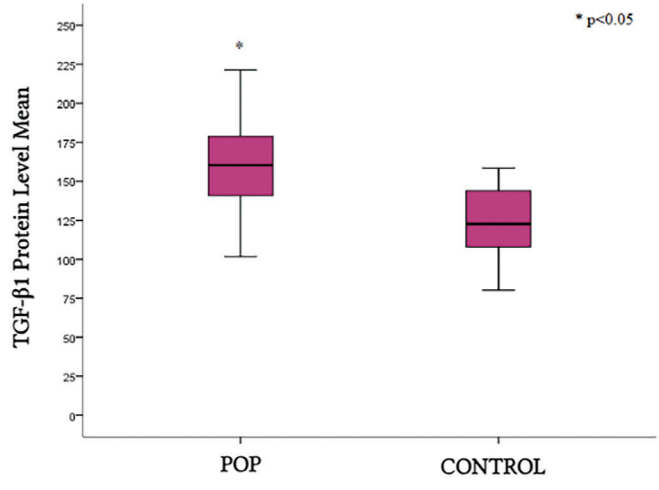

Figure 2. TGF-β1 protein level

POP: Pelvic organ prolapse, TGF-β1: Type I and transforming growth factor-beta 1

Table 3. Collagen type I and TGF-β1 protein levels in POP and control groups

Proteins	POP (mean ± SD)	Controls (mean ± SD)	p*
TGF-β1	59.38±41.44	125.06±20.76	**0.000**
Collagen type I	76.48±15.27	72.02±11.92	0.091

*: Mann-Whitney U test, SD: Standard deviation, POP: Pelvic organ prolapse, TGF-β1: Type I and transforming growth factor-beta 1

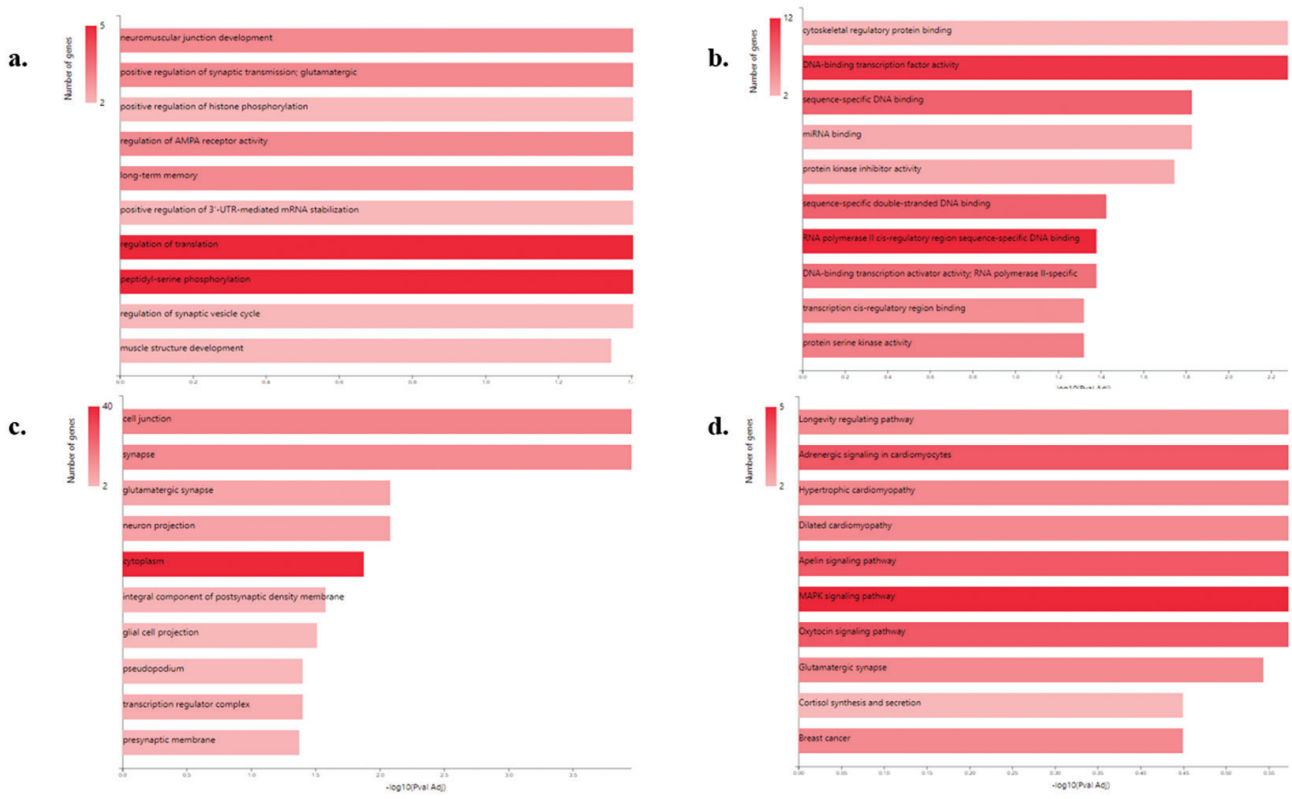

Figure 3. GO and pathway analysis of miR-129-5p target genes **a.** Biological process **b.** Molecular function **c.** Cellular component **d.** Pathway analysis (KEGG pathway)

GO: Gene ontology

levels were observed between the groups, with heightened levels noted in severe POP cases relative to mild or common presentations.[18] In our thesis investigation, a notable elevation of TGF-β1 protein levels by a factor of 1.2 was detected in POP patients in contrast to the control cohort (p=0.000). Moreover, findings by Carlin et al.[18] corroborated our study, revealing escalated TGF-β1 levels within the subset of high-severity POP patients. These collective observations underscore the nuanced role of TGF-β1 in the pathogenesis and severity stratification of POP, delineating varying expressions across distinct clinical contexts.

In an in-depth investigation of the anterior vaginal wall and USL, it was demonstrated that individuals with POP exhibited a more fragmented and irregular collagen structure compared to their non-affected counterparts. Additionally, a decrease in the expression of collagen type I and collagen type III was noted within the patient group.[19] In a POP study conducted by Vetuschi et al.,[20] a reduction in collagen type I expression level was observed in sagging tissues, while an increase in collagen type III expression level was noted. These variations in collagen levels are believed to disrupt the dynamic functionality of the pelvic floor.[20] However, findings by Kerkhof et al.[21] contradicted these observations, revealing no significant differences in collagen type I, III, and IV levels between the POP and control groups. In our study, although collagen type I protein levels were higher in POP patients than in the control group, the results were not statistically significant (p=0.091). However, our results are consistent with some studies in the literature and emphasize the complex and multifactorial nature of collagen dynamics in POP pathogenesis.

In endometriosis tissues, a gynecological disease that poses a serious health problem for women, NEAT1 was shown to be overexpressed while the expression of miR-124-3p was reduced. Consequently, NEAT1 was found to promote malignant behavior in endometriosis by targeting miR-124-3p.[22] NEAT1, which is believed to be involved in the pathogenesis of gynecologic diseases, has rarely been studied in polycystic ovary syndrome (PCOS). Wu et al.[23] investigated the role of miR-324-3p, NEAT1 and bromodomain-containing 3 (BRD3) in PCOS tissues and PCOS mouse models. They found that the expression levels of NEAT1 and BRD3 were high, while the expression levels of miR-324-3p were low, particularly in the tissues of women with PCOS. Mechanistically, it was shown that NEAT1 targets miR-324-3p, miR-324-3p targets BRD3, and the high levels of NEAT1 and

BRD3, along with the low levels of miR-324-3p, increase PCOS severity.[23] In our thesis study, although the mean expression of NEAT1 in patients with POP was higher compared to the control group, the results were not statistically significant (p=0.492). While studies in the literature indicate an association between NEAT1 and gynecological diseases, our findings suggest that NEAT1 is not associated with POP.

A study has shown that miR-19-3p is upregulated in the tissues of individuals with POP, while IGF-1 and collagen type I expressions are downregulated. It has been suggested that miR-19-3p may affect collagen type I synthesis in POP by targeting IGF-1.[24] Uterine leiomyomas, or fibroids, are a gynecological disease affecting 30-50% of women of reproductive age, characterized by symptoms such as heavy menstrual bleeding, pelvic pain, and pressure. miR-139-5p, which exhibits tumor-suppressing properties, has been shown to be decreased in uterine leiomyomas, correlating with increased collagen type I expression.[25] Feng et al.[26] found that miR-139-5p expression is significantly upregulated in endometrial stromal cells in endometriosis.

Cervical intraepithelial neoplasia, caused by human papillomavirus, is known to be influenced by miRNAs. Zhang et al.[27] demonstrated that miR-129-5p levels decrease proportionally with the progression of cervical intraepithelial lesions. In intervertebral disc degeneration, miR-129-5p levels are lower compared to control groups. Additionally, miR-129-5p carried in extracellular vesicles from mesenchymal stem cells reduces apoptosis, ECM degradation, and M1 macrophage polarization in the nucleus pulposus tissues of patients with intervertebral disc degeneration.[28]

Renal fibrosis has been shown to involve the determination of miR-129-5p by NEAT1, leading to the excessive accumulation of collagen type I which a main target of miR-129-5p.[29] In diabetic wound healing, miR-129-5p has been demonstrated to regulate specificity protein-1, a transcription factor involved in MMP-9 expression, significantly decreasing MMP-9 levels.[30] In our study, although the miR-139-5p expression level was higher in the control group, it was not statistically significant (p=0.570). Additionally, miR-129-5p levels were found to be 1.9-fold higher in POP tissues compared to controls, with the results being statistically significant (p=0.011). While miR-139-5p is associated with endometriosis, our findings indicate no significant relationship with POP. The results for miR-129-5p align with those reported in studies on cervical intraepithelial neoplasia.

CONCLUSION

Our study show that the expression levels of miR-129-5p and TGF-β1 protein were higher in patients with POP compared to control individuals. Previous studies have shown conflicting results regarding collagen levels in POP, with reports of both increases and decreases. It is known that an increase in miR-129-5p levels decreases collagen type I levels, while an increase in TGF-β1 levels increases collagen type I levels. Our study suggests that the concurrent increase in miR-129-5p and TGF-β1 levels may result in no net change in collagen type I levels. Additionally, the higher expression of TGF-β1 in the patient group may be associated with the severity of POP, as TGF-β1 is more highly expressed in severe cases compared to mild cases.

This study lays the groundwork for future research on POP. Future studies could investigate other lncRNAs that target miR-129-5p to further elucidate their relationship with POP. Additionally, identifying other target genes of miR-129-5p and exploring their roles in POP could provide deeper insights. Investigating other miRNAs that target TGF-β1 and evaluating their relationships with POP would also be valuable. Future research should focus on identifying molecules that regulate these genes and conducting epigenetic regulation analyses, which could help identify potential biomarkers for POP.

ETHICS

Ethics Committee Approval: The study was approved by the Clinical Research Ethics Committee of Muğla Sıtkı Koçman University (approval number: 19/II, date: 15.09.2021).

Informed Consent: Informed consent was obtained from all participants prior to their inclusion in the study.

FOOTNOTES

Contributions

Concept: A.D.B., B.K., B.S., M.N.A., E.A., Ç.Ö., T.E., Design: A.D.B., B.K., B.S., M.N.A., E.A., Ç.Ö., T.E., Data Collection or Processing: B.K., B.S., M.N.A., E.A., Analysis or Interpretation: A.D.B., Ç.Ö., T.E., Literature Search: A.D.B., B.K., B.S., M.N.A., E.A., Ç.Ö., T.E., Writing: A.D.B., B.K., B.S., M.N.A., E.A., Ç.Ö., T.E.

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REFERENCES

1. Budinurdjaja P, Arsana Wiyasa IW, Oktaviyanti IK, Sargowo D. Search for aglycone isoflavone from soybean as candidate for pelvic organ prolapse treatment: In silico study of TGF-β1, Hsp70, and Bcl-xl signals. Clinical Nutrition Experimental. 2019; 23: 15-22.

2. Obsa MS, Worji TA, Kedir NA, Kute NG. Risk factors of pelvic organ prolapse at asella teaching and referral hospital: unmatched case control study. Front Glob Womens Health. 2022; 3: 833823.

3. Weintraub AY, Glinter H, Marcus-Braun N. Narrative review of the epidemiology, diagnosis and pathophysiology of pelvic organ prolapse. Int Braz J Urol. 2019; 46: 5-14.

4. Kerkhof MH, Hendriks L, Brölmann HA. Changes in connective tissue in patients with pelvic organ prolapse--a review of the current literature. Int Urogynecol J Pelvic Floor Dysfunct. 2009; 20: 461-74.

5. Sugaya K, Kadekawa K, Ashitomi K, Nishijima S, Matsumoto S. Plasma levels of transforming growth factor-beta 1 in women with pelvic organ prolapse. Open Journal of Urology. 2023; 13: 133-42.

6. Li Y, Kowdley KV. MicroRNAs in common human diseases. Genomics Proteomics Bioinformatics. 2012; 10: 246-53.

7. Wu YY, Kuo HC. Functional roles and networks of non-coding RNAs in the pathogenesis of neurodegenerative diseases. J Biomed Sci. 2020; 27: 49.

8. Cheng C, Spengler RM, Keiser MS, et al. The long non-coding RNA NEAT1 is elevated in polyglutamine repeat expansion diseases and protects from disease gene-dependent toxicities. Hum Mol Genet. 2018; 27: 4303-14.

9. Donati S, Ciuffi S, Brandi ML. Human circulating miRNAs real-time qRT-PCR-based analysis: an overview of endogenous reference genes used for data normalization. Int J Mol Sci. 2019; 20: 4353.

10. Carmona-Saez P, Chagoyen M, Tirado F, Carazo JM, Pascual-Montano A. GENECODIS: a web-based tool for finding significant concurrent annotations in gene lists. Genome Biol. 2007; 8: R3.

11. Ferrazzi E, Bulfamante G, Mezzopane R, et al. Uterine Doppler velocimetry and placental hypoxic-ischemic lesion in pregnancies with fetal intrauterine growth restriction. Placenta. 1999; 20: 389-94.

12. Nakad B, Fares F, Azzam N, Feiner B, Zilberlicht A, Abramov Y. Estrogen receptor and laminin genetic polymorphism among women with pelvic organ prolapse. Taiwanese J Obst Gynecol. 2017; 56: 750-4.

13. McKee TJ, Perlman G, Morris M, Komarova SV. Extracellular matrix composition of connective tissues: a systematic review and meta-analysis. Sci Rep. 2019; 9: 10542.

14. Kim KK, Sheppard D, Chapman HA. TGF-β1 signaling and tissue fibrosis. Cold Spring Harb Perspect Biol. 2018; 10: a022293.

15. Qi XY, Hong L, Guo FQ, et al. Expression of transforming growth factor-beta 1 and connective tissue growth factor in women with pelvic organ prolapse. Saudi Med J. 2011; 32: 474-8.

16. Li BS, Hong L, Min J, et al. The expression of glutathione peroxidase-1 and the anabolism of collagen regulation pathway transforming growth factor-beta1-connective tissue growth factor in women with uterine prolapse and the clinic significance. Clin Exp Obstet Gynecol. 2013; 40: 586-90.

17. Akin MN, Sivaslioglu AA, Edgunlu T, Kasap B, Celik SK. SMAD2, SMAD3 and TGF-β gene expressions in women suffering from urge urinary incontinence and pelvic organ prolapse. Mol Biol Rep. 2021; 48: 1401-7.

18. Carlin GL, Bodner K, Kimberger O, et al. The role of transforming growth factor-ß (TGF-ß1) in postmenopausal women with pelvic organ prolapse: An immunohistochemical study. Eur J Obstet Gynecol Reprod Biol X. 2020; 7: 100111.

19. Zeng C, Liu J, Wang H, et al. Correlation between autophagy and collagen deposition in patients with pelvic organ prolapse. Female Pelvic Med Reconstr Surg. 2018; 24: 213-21.

20. Vetuschi A, D'Alfonso A, Sferra R, et al. Changes in muscularis propria of anterior vaginal wall in women with pelvic organ prolapse. Eur J Histochem. 2016; 60: 2604.

21. Kerkhof MH, Ruiz-Zapata AM, Bril H, et al. Changes in tissue composition of the vaginal wall of premenopausal women with prolapse. Am J Obstet Gynecol. 2014; 210: 168.e1-9.

22. Yuan D, Zhu D, Yin B, et al. Expression of lncRNA NEAT1 in endometriosis and its biological functions in ectopic endometrial cells as mediated via miR-124-3p. Genes Genomics. 2022; 44: 527-37.

23. Wu L, Tu Z, Bao Y, Zhai Q, Jin L. Long noncoding RNA NEAT1 decreases polycystic ovary syndrome progression via the modulation of the microRNA-324-3p and BRD3 axis. Cell Biol Int. 2022; 46: 2075-84.

24. Yin Y, Qin M, Luan M, Xia Z. miR-19-3p promotes autophagy and apoptosis in pelvic organ prolapse through the AKT/mTOR/p70S6K pathway: function of miR-19-3p on vaginal fibroblasts by targeting IGF-1. Female Pelvic Med Reconstr Surg. 2021; 27: e630-8.

25. Ahn SH, Kim H, Lee I, et al. MicroRNA-139-5p regulates fibrotic potentials via modulation of collagen type 1 and phosphorylated p38 MAPK in uterine leiomyoma. Yonsei Med J. 2021; 62: 726-33.

26. Feng L, Chen X, Zhang S, Chen Y, Yu Y. Role of miR-139-5p in ectopic endometrial stromal cells and the underlying molecular mechanism. Exp Ther Med. 2021; 22: 1251.

27. Zhang J, Li S, Yan Q, et al. Interferon-β induced microRNA-129-5p down-regulates HPV-18 E6 and E7 viral gene expression by targeting SP1 in cervical cancer cells. PLoS One. 2013; 8: e81366.

28. Cui S, Zhang L. microRNA-129-5p shuttled by mesenchymal stem cell-derived extracellular vesicles alleviates intervertebral disc degeneration via blockade of LRG1-mediated p38 MAPK activation. J Tissue Eng. 2021; 12: 20417314211021679.

29. Li C, Liu YF, Huang C, et al. Long noncoding RNA NEAT1 sponges miR-129 to modulate renal fibrosis by regulation of collagen type I. Am J Physiol Renal Physiol. 2020; 319: F93-105.

30. Wang W, Yang C, Wang XY, et al. MicroRNA-129 and -335 promote diabetic wound healing by inhibiting Sp1-mediated MMP-9 expression. Diabetes. 2018; 67: 1627-38.