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COLLAGEN FIBRE ARCHITECTURE AND PROTEOGLYCAN DISTRIBUTION IN FEMALE KNEE MENISCI ACROSS REPRODUCTIVE AND POST-REPRODUCTIVE AGE GROUPS

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INTRODUCTION

The structural integrity of the knee meniscus depends on the precise spatial organisation of its extracellular matrix, composed primarily of type I collagen arranged in circumferential, radial, and surface-oriented fibre bundles, interpenetrated by a proteoglycan-rich ground substance whose hydrophilic properties confer the viscoelastic behaviour essential for meniscal load-transmission and shock-absorption functions (Fox et al., 2015; Makris et al., 2011). Proteoglycans — predominantly aggrecan, biglycan, and decorin — interact electrostatically with water molecules to generate the swelling pressure that resists compressive loading, while collagen fibres bear the circumferential tensile (hoop) stresses generated during axial loading of the knee (Berthiaume et al., 2005; Messner & Gao, 1998).

Ageing exerts differential and region-specific effects on these matrix components. Evidence from biochemical and histochemical studies indicates progressive proteoglycan depletion with age, particularly in the avascular inner zone of the meniscus where matrix turnover is already limited by the absence of vascular supply (Ingman et al., 1974; Fithian et al., 1990). Collagen fibre disorganisation — manifesting as loss of circumferential alignment, increased inter-fibre spacing, and eventually frank fibre fragmentation — is thought to underlie the mechanical weakening that predisposes ageing menisci to horizontal cleavage tears and complex degenerative lesions (Englund et al., 2012).

Sex-specific differences in this ageing process have been incompletely characterised. The influence of female sex hormones — particularly oestrogen — on meniscal matrix homeostasis is supported by the

identification of oestrogen receptors in meniscal fibrochondrocytes and by epidemiological data demonstrating accelerated meniscal and cartilaginous degeneration following natural or surgical menopause (Liu et al., 2016; Hanna et al., 2010). However, systematic histomorphometric data on collagen architecture and proteoglycan distribution across the female reproductive lifespan, including the perimenopausal and postmenopausal periods, remain limited in the published literature.

The present study aimed to provide a quantitative histomorphometric characterisation of collagen fibre architecture and proteoglycan distribution in female knee menisci across four age-defined groups spanning the reproductive and post-reproductive periods, with the hypothesis that the most pronounced matrix deterioration would be observed in the perimenopausal and postmenopausal decades.

MATERIALS AND METHODS

Meniscal specimens were obtained from 112 women at the Republican Specialised Scientific and Practical Medical Centre of Traumatology and Orthopaedics, Tashkent, Uzbekistan, between 2021 and 2025. The study group comprised intraoperative specimens from total knee arthroplasty and arthroscopic procedures (n = 72) and cadaveric preparations from autopsy (n = 40). Participants were stratified by age: Group A (reproductive period, 25–44 years, n = 28), Group B (perimenopausal period, 45–54 years, n = 30), Group C (early postmenopause, 55–64 years, n = 28), Group D (late postmenopause, 65–80 years, n = 26). Exclusion criteria included rheumatoid arthritis, crystal arthropathies, prior knee surgery, and systemic corticosteroid therapy.

Specimens were fixed in 10% neutral-buffered formalin for 48 hours, processed through graded ethanol series and xylene, embedded in paraffin, and sectioned at 5 µm thickness in three orientations (longitudinal, transverse, and coronal). Sections were stained with Masson's trichrome for collagen visualisation, Safranin-O/Fast Green for proteoglycans, Alcian Blue (pH 2.5) for sulphated glycosaminoglycans, and Picrosirius Red (examined under polarised light) for collagen fibre type and organisation. Quantitative image analysis was performed using ImageJ software on digitised histological slides (magnification ×100 and ×200). Parameters

assessed included: collagen fibre alignment index (circular standard deviation of fibre orientation angles), collagen fibre bundle diameter, Safranin-O staining intensity (optical density), and zonal distribution of proteoglycan content (inner, middle, and outer thirds of the meniscus). Statistical analysis used one-way ANOVA with Bonferroni post-hoc correction; significance threshold $p < .05$.

RESULTS

Collagen fibre architecture. Picrosirius Red staining under polarised light revealed a progressive loss of organised birefringence with advancing age, indicating disruption of type I collagen fibre alignment. The collagen fibre alignment index (higher values indicating greater disorganisation) increased significantly across groups: Group A: 12.4° ± 3.1°; Group B: 19.7° ± 4.3°; Group C: 28.6° ± 5.8°; Group D: 41.3° ± 7.4° ($F(3,108) = 89.4$; $p < .001$). Post-hoc analysis confirmed significant differences between all adjacent group pairs ($p < .01$ for A vs. B; $p < .001$ for B vs. C and C vs. D). Collagen fibre bundle diameter showed a statistically significant reduction in Groups C and D compared with Groups A and B (mean: 18.7 ± 2.4 µm in Group A vs. 11.2 ± 2.1 µm in Group D; $p < .001$), consistent with progressive fibre thinning and fragmentation.

Proteoglycan distribution. Safranin-O staining intensity was highest in the inner zone of the meniscus across all age groups, consistent with the known zonal variation in proteoglycan content. Quantitative optical density analysis revealed progressive reduction in Safranin-O staining intensity with age: Group A outer zone: 0.61 ± 0.08; Group D outer zone: 0.29 ± 0.06 ($p < .001$). The inner zone showed the most pronounced age-related depletion: optical density declined from 0.89 ± 0.09 in Group A to 0.31 ± 0.07 in Group D ($p < .001$), representing a 65% reduction across the age range studied. Alcian Blue staining confirmed parallel depletion of sulphated glycosaminoglycans, particularly in the inner and middle zones from Group C onwards.

Zonal analysis. The inner avascular zone demonstrated significantly greater age-related matrix deterioration than the outer vascular zone across all parameters, consistent with its limited capacity for matrix repair. A significant interaction between age group and meniscal zone was observed

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for proteoglycan content ($F(9,324) = 12.7$; $p < .001$), confirming that inner zone depletion accelerated disproportionately in Groups C and D.

Between-meniscus differences. Medial menisci demonstrated significantly greater collagen disorganisation (alignment index: 28.9° ± 6.2° vs. 24.1° ± 5.8° for lateral menisci across all groups combined; $p < .05$) and proteoglycan depletion in the inner zone (optical density: 0.54 ± 0.11 vs. 0.61 ± 0.09; $p < .05$), consistent with greater biomechanical loading in the medial compartment.

DISCUSSION

The present study provides detailed quantitative evidence of progressive, zone-specific deterioration in collagen fibre architecture and proteoglycan content in female menisci across the reproductive and post-reproductive lifespan. The most important clinical finding is the acceleration of matrix deterioration at the perimenopausal-to-postmenopausal transition (Groups B to C), consistent with the established role of oestrogen in regulating meniscal matrix metabolism (Liu et al., 2016; Bellido et al., 2010).

The pronounced inner zone proteoglycan depletion observed in postmenopausal groups has specific mechanical significance: loss of proteoglycan-bound water from the inner zone reduces the hydrostatic pressure component of load resistance, increasing the proportion of compressive load borne by the solid collagen network and predisposing to collagen fibre fatigue failure — a plausible mechanistic pathway for the increased incidence of horizontal cleavage tears in postmenopausal women (Englund et al., 2012; Messner & Gao, 1998).

The greater degenerative burden in medial versus lateral menisci corroborates biomechanical data indicating that the medial compartment bears approximately 60–70% of the total knee joint load (Berthiaume et al., 2005), making the medial meniscus more susceptible to cumulative age-related matrix fatigue. This finding has direct clinical relevance for the interpretation of MRI findings in postmenopausal women with knee pain.

CONCLUSION

Quantitative histomorphometric analysis demonstrates progressive, zone-specific deterioration of collagen fibre architecture and proteoglycan content

in female knee menisci, with a marked acceleration during the perimenopausal transition. The inner avascular zone of the medial meniscus represents the site of earliest and most severe matrix depletion. These findings provide a structural basis for the elevated risk of meniscal tears and knee osteoarthritis in postmenopausal women and support the investigation of oestrogen-related matrix protective strategies as potential preventive interventions.

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