The Biomechanical Properties of Human Menisci as a Basis for Future Replacement Designs: A Systematic Review

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INTRODUCTION: Accurate mechanical characterization of meniscal tissue *in-vitro* remains a critical need, particularly for the development of suitable tissue-engineered meniscus replacements and for rigorous evaluation of the mechanical function of the construct *ex-vivo* [1]. To date, a wide variety of test configurations (unconfined, confined, indentation), modes (stress relaxation, creep, cyclic), and test protocols exist with marked differences in sample collection and preservation, sample geometry and dimensions, loading rates, post-processing routines, and cohort demographics. Because of this variety of potential influencing factors, it is difficult to attribute the origin of the wide range of reported material parameters either to specific differences in testing protocols or to the structural inhomogeneity of the meniscal tissue itself, which appears to vary even more with increasing age or degree of degeneration of the specimen. Consequently, the key challenge for tissue engineers is to identify the actual mechanical properties of the native meniscus that their constructs should mimic. Therefore, the purpose of this systematic review was to identify test-specific characteristics that contribute to uncertainties in the estimation of mechanical properties of the human meniscus and its attachments derived from common quasi-static and dynamic tests in tension, compression and shear.

METHODS: This review was conducted following the PRISMA statement [2]. A comprehensive electronic database search was performed on PubMed, Web of Science, Cochrane Library and Science Direct. The eligibility criteria were designed to address the following guiding question (PCO) [3]: How do variations in the testing protocols commonly used for biomechanical testing (Comparison) affect the determination of mechanical properties (Outcome) of the human meniscus and its root attachments (Population)? Maximum sensitivity was applied to the search strategy to reduce the risk of missing pertinent studies.

RESULTS: The electronic search revealed a total of 3770 records, with 53 studies remaining after application of the exclusion criteria (Fig.1), comprising studies that performed quasi-static (tension: n=22; compression: n=26; shear: n=1) and/or dynamic tests (tension: n=2; compression: n=8; shear: n=4). The circumferential elastic tensile modulus E_T showed up to tenfold differences (Fig. 3A) in all regions of the meniscus body (Fig. 2A). In general, authors examining entire meniscus specimens (Fig. 2B) reported on average 58% lower circumferential E_T (Fig. 3A) than authors investigating standardized isolated specimens (Fig. 2A). Moreover, the axial elastic compression modulus E_C was strongly dependent on the mathematical model used for evaluation, the applied load level and the strain at evaluation, ranging from 0.06 MPa to 353.40 MPa. Depending on the study-specific test configuration and mode, including the definition of the equilibrium modulus E_{Eq} (instantaneous modulus E_{Inst}), up to tenfold (fivefold) differences in E_{Eq} (E_{Inst}) were reported for all meniscus body regions (Fig. 3B). In contrast to the rather consistently reported aggregate modulus, hydraulic permeability k was on average 28 times higher when the specimen was compressed with the surface of the mid-material contacting the porous plug instead of the femoral or tibial superficial layer (Fig. 3C). For the dynamic shear properties, up to 10^{-6} differences in both storage moduli and loss moduli were reported depending on the test frequency. In general, the reported dynamic shear modulus was on average an order of magnitude lower than the dynamic compression modulus (0.05 MPa vs. 0.76 MPa).

DISCUSSION: Strong evidence was found that the large differences in biomechanical properties of the meniscus were mainly attributable to variations in test setup, test protocol, and cohort demographics. For tensile testing, the most critical factors influencing the outcome measures were identified as specimen geometry (dumbbell vs. rectangular vs. non-standard) and thickness (0.1–7.8 mm), slippage prevention (sandpaper vs. special clamps), method of strain measurement (grip-to-grip vs. digital image correlation), and the strain rate (0.15–100% l0/min). In contrast, for compression testing, the test configuration and mode, predefined relaxation criteria (70–7200 s), post-processing of the experimental data in terms of mathematical model selection including numerical fitting methods have been found to be the most sensitive characteristics. Especially in confined compression setups, the boundary conditions of both the interdigitation contact between the indenter and the tissue, the porosity of the indenter, and the level of confinement present at the sidewall of the specimen strongly affect the recorded stress-strain data. Besides keeping freeze-thaw cycles minimal [4], temperature and hydration (reported in 39/53 studies) should be controlled to mimic the physiological environment of the meniscus in the knee joint. High ionic concentrations of saline have been shown to induce up to 20% osmotic swelling of the meniscus, resulting in impaired compressive properties [5]. Therefore, the effect of the bathing solution should be considered and ideally mimic the osmotic and ionic properties of synovial fluid. While 94% of the authors reported the age of the specimen, 10/53 provided further information on the degeneration condition. It has been shown that the tensile properties of the meniscus are not affected by progressive knee joint degeneration, but profound and contradictory changes in the compressive properties associated with age and degeneration have been reported [6]. In conclusion, future studies should consider the specimen-related effects of age and degeneration, storage, temperature and hydration on the outcome measures, while providing detailed information on the testing protocol used, including post processing routines, to allow for better interpretation by the reader.

SIGNIFICANCE/CLINICAL RELEVANCE: This work highlights the unmet need for standardization and reporting guidelines for mechanical characterization of meniscal tissue. Currently, it is essential for authors investigating the mechanical properties of potential meniscal replacements and biomaterials to have a control group, rather than a direct comparison to moduli reported in the literature, to eliminate the uncertainty of different test environments and protocols.

REFERENCES: [1] Klarmann et al., *Biomaterials and Biosystems*, 4, 100026, 2021; [2] Moher et al., *PLOS Med.*, 6(7), 1000097, 2009; [3] Liberati et al., *J. Clin. Epidemiol.*, 62(10), 1-34, 2009; [4] Lewis et al., *J. Orthop, Res.*, 26(1), 49-55, 2008; [5] Mahmood et al., *Clin. Biomech.*, 77, 105028, 2020; [6] Fischenich et al., *J. Biomech.*, 48, 1407-1411, 2015

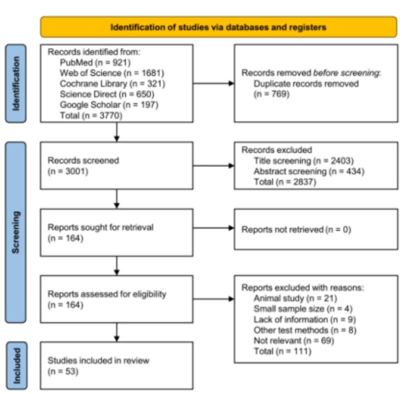

Fig. 1: Modified PRISMA flowchart of the study selection process. Last update on 2023/01/12.

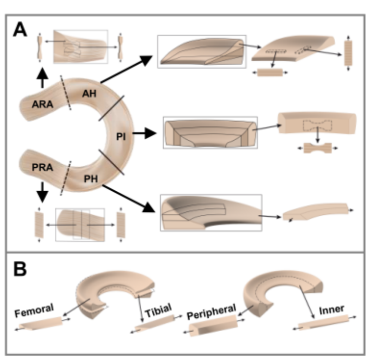

Fig. 2: Study-specific specimen collection with respect to subdivision in regional zones and layers for tensile testing. A: Standardized dumbbell-shaped or rectangular specimens. B: Specimen collection from the entire meniscal body.

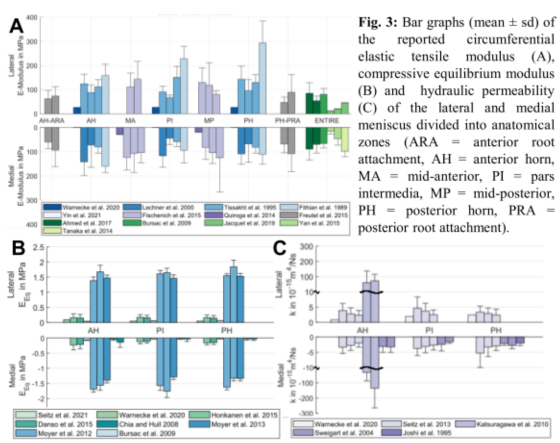

Fig. 3: Bar graphs (mean ± sd) of the reported circumferential elastic tensile modulus (A), compressive equilibrium modulus (B) and hydraulic permeability (C) of the lateral and medial meniscus divided into anatomical zones (ARA = anterior root attachment, AH = anterior horn, MA = mid-anterior, PI = pars intermedia, MP = mid-posterior, PH = posterior horn, PRA = posterior root attachment).