Bone & Joint Research

Supplementary Material

10.1302/2046-3758.1312.BJR-2024-0020.R1

Supplementary Information – search strategy

Database: Medline (Ovid MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE) 1946 to present

Search strategy:

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1 exp Proteoglycans/ (39384)

2 exp Elasticity/ (50892)

3 (elasticity or "elastic modulus" or topograph* or anisotrop*).ti,ab. (160630)

4 exp Extracellular Matrix/ (47818)

5 "extracellular matri*".ti,ab. (106140)

6 exp Extracellular Matrix Proteins/ (193763)

7 (Aggrecan* or "Cartilage Specific Proteoglycan Core Proteins" or COMP or "Thrombospondin 5" or TSP5 or collagen* or pro-collagen* or procollagen or tropocollagen* or fibulin* or "alpha-collagen" or elastin* or thropoelastin* or fibrillin* or fibronectin* or glycoprotein* or laminin* or "glycoprotein GP-2" or "latent TGF beta binding protein" or matrilin* or MATN* or "matrix protein*" or netrin* or netrin-1 or biglycan* or decorin* or hyalectin* or neurocan* or fibromodulin* or lumican* or tenacin* or tenacin-c or cytotactin* or hexabrachion* or versican* or "chondroitin sulfate proteoglycan core protein 2" or "chondroitin sulphate proteoglycan core protein 2" or vitronectin* or pyridinoline* or hydroxylysylpyridinoline*).ti,ab. (448428)

8 microfibril*.ti,ab. (4325)

9 exp Glycosaminoglycans/ (121397)

10 (glycosaminoglycan* or mucopolysaccharide* or proteoglycan* or chondroitin or translagen or blutal or heparin or "heparinic acid" or heparitin or heparan or "hyaluronic acid" or hyaluron*n or hyaluronate or keratan or keratosulphate or keratosulfate).ti,ab. (160866)

11 Calcinosis/ (38846)

12 (calcinosis or calcinoses or calcification* or microcalcification* or microcalcinosis or microcalcinoses or hydroxyapatite or hydroxylapatite).ti,ab. (93466)

13 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 (1009050)

14 exp Intervertebral Disc/ (15222)

15 ("intervertebral dis*" or "annulus fibrosus" or "anulus fibrosis" or "nucleus pulposus").ti,ab. (18128)

16 exp Ligaments, Articular/ (32725)

17 ligament*.ti,ab. (85003)

18 exp Muscle, Skeletal/ (283110)

19 muscle*.ti,ab. (744181)

20 exp Tendons/ (44653)

21 tendon*.ti,ab. (70548)

22 Menisci, Tibial/ (7362)

23 (menisc* or "semilunar cartilage*").ti,ab. (18889)

24 exp Joint Capsule/ (29528)

25 ("joint capsule*" or "articular capsule*" or "capsula articularis" or "synovial capsule*" or "synovial fold*" or "synovial plica*" or "hip capsule*" or "knee capsule*" or "shoulder capsule*").ti,ab. (3859)

26 Bursa, Synovial/ (1124)

27 ("synovial bursa*" or synovium or "synovial membrane*").ti,ab. (11261)

28 exp Adipose Tissue/ (103687)

29 ("adipose tissue*" or "body fat*" or "body pad*" or "fat* tissue*" or "fat pad*").ti,ab. (123620)

30 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 (1173134)

31 exp Osteoarthritis/ (68777)

32 (osteoarthr* or "degenerative arthri*" or arthroses or arthrosis).ti,ab. (85531)

33 31 or 32 (105393)

34 13 and 30 and 33 (4268)

35 34 (4268)

36 limit 35 to yr="2020 - 2021" (490)

Database: Embase 1974 to present

Search strategy:

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1 proteoglycan/ (24376)

2 exp elasticity/ (69514)

3 (elasticity or "elastic modulus" or topograph* or anisotrop*).ti,ab. (166957)

4 exp extracellular matrix/ (153794)

5 "extracellular matri*".ti,ab. (134542)

6 exp scleroprotein/ (346147)

7 (Aggrecan* or "Cartilage Specific Proteoglycan Core Proteins" or COMP or "Thrombospondin 5" or TSP5 or collagen* or pro-collagen* or procollagen or tropocollagen* or fibulin* or "alpha-collagen" or elastin* or thropoelastin* or fibrillin* or fibronectin* or glycoprotein* or laminin* or "glycoprotein GP-2" or "latent TGF beta binding protein" or matrilin* or MATN* or "matrix protein*" or netrin* or netrin-1 or biglycan* or decorin* or hyalectin* or neurocan* or fibromodulin* or lumican* or tenacin* or tenacin-c or cytotactin* or hexabrachion* or versican* or "chondroitin sulfate proteoglycan core protein 2" or "chondroitin sulphate proteoglycan core protein 2" or vitronectin* or pyridinoline* or hydroxylysylpyridinoline*).ti,ab. (555848)

8 microfibril*.ti,ab. (4450)

9 exp glycosaminoglycan/ (250102)

10 (glycosaminoglycan* or mucopolysaccharide* or proteoglycan* or chondroitin or translagen or blutal or heparin or "heparinic acid" or heparitin or heparan or "hyaluronic acid" or hyaluron*n or hyaluronate or keratan or keratosulphate or keratosulfate).ti,ab. (203041)

11 exp calcinosis/ (16203)

12 (calcinosis or calcinoses or calcification* or microcalcification* or microcalcinosis or microcalcinoses or hydroxyapatite or hydroxylapatite).ti,ab. (118865)

13 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 (1369541)

14 exp intervertebral disk/ (16400)

15 ("intervertebral dis*" or "annulus fibrosus" or "anulus fibrosis" or "nucleus pulposus").ti,ab. (21310)

16 exp joint ligament/ (28620)

17 ligament*.ti,ab. (103603)

18 exp skeletal muscle/ (367283)

19 muscle*.ti,ab. (919762)

20 exp tendon/ (41624)

21 tendon*.ti,ab. (82988)

22 knee meniscus/ (10357)

23 (menisc* or "semilunar cartilage*").ti,ab. (22980)

24 joint capsule/ (3803)

25 ("joint capsule*" or "articular capsule*" or "capsula articularis" or "synovial capsule*" or "synovial fold*" or "synovial plica*" or "hip capsule*" or "knee capsule*" or "shoulder capsule*").ti,ab. (4819)

26 synovial bursa/ (2550)

27 ("synovial bursa*" or synovium or "synovial membrane*").ti,ab. (15675)

28 exp adipose tissue/ (176340)

29 ("adipose tissue*" or "body fat*" or "body pad*" or "fat* tissue*" or "fat pad*").ti,ab. (166084)

30 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 (1411380)

31 exp osteoporosis/ (138070)

32 (osteoarthr* or "degenerative arthri*" or arthroses or arthrosis).ti,ab. (119642)

33 31 or 32 (253893)

34 13 and 30 and 33 (6543)

35 34 (6543)

36 limit 35 to yr="2020 - 2021" (909)

Scopus

((TITLE-ABS-KEY (elasticity OR "elastic modulus" OR topograph* OR anisotrop* OR "extracellular matri*" OR aggrecan* OR "Cartilage Specific Proteoglycan Core Proteins" OR comp OR "Thrombospondin 5" OR tsp5 OR collagen* OR pro-collagen* OR procollagen OR tropocollagen* OR fibulin* OR "alpha-collagen" OR elastin* OR thropoelastin* OR fibrillin* OR fibronectin* OR glycoprotein* OR laminin* OR "glycoprotein GP-2" OR "latent TGF beta binding protein" OR matrilin* OR matn* OR "matrix protein*" OR netrin* OR netrin-1 OR biglycan* OR decorin* OR hyalectin* OR neurocan* OR fibromodulin* OR lumican* OR tenacin* OR tenacin-c OR cytotactin* OR hexabrachion* OR versican* OR "chondroitin sulfate proteoglycan core protein 2" OR "chondroitin sulphate proteoglycan core protein 2" OR vitronectin* OR pyridinoline* OR hydroxylysylpyridinoline*) OR TITLE-ABS-KEY (microfibril* OR glycosaminoglycan* OR mucopolysaccharide* OR proteoglycan* OR chondroitin OR translagen OR blutal OR heparin OR "heparinic acid" OR heparitin OR heparan OR "hyaluronic acid" OR hyaluron*n OR hyaluronate OR keratan OR keratosulphate OR keratosulfate OR calcinosis OR calcinoses OR calcification* OR microcalcification* OR microcalcinosis OR microcalcinoses OR hydroxyapatite OR hydroxylapatite))) AND ((TITLE-ABS-KEY (("intervertebral dis*" OR "annulus fibrosus" OR "anulus fibrosis" OR "nucleus pulposus")) OR TITLE-ABS-KEY (ligament* OR muscle* OR tendon* OR menisc* OR "semilunar cartilage*" OR ("joint capsule*" OR "articular capsule*" OR "capsula articularis" OR "synovial capsule*" OR "synovial fold*" OR "synovial plica*" OR "hip capsule*" OR "knee capsule*" OR "shoulder capsule*") OR ("synovial bursa*" OR synovium OR "synovial membrane*") OR ("adipose tissue*" OR "body fat*" OR "body pad*" OR "fat* tissue*" OR "fat pad*")))) AND (TITLE-ABS-KEY (osteoarthr* OR "degenerative arthri*" OR arthroses OR arthrosis)) AND (LIMIT-TO (PUBYEAR , 2022) OR LIMIT-TO (PUBYEAR , 2021) OR LIMIT-TO (PUBYEAR , 2020))

Table i. Structural extracellular matrix components and architectural features in non-cartilage soft tissues of human osteoarthritic joints.

Tissue	ECM feature	Change vs control	Description of feature in OA tissue	Measurement technique(s)	Analysis	Stat. test	Ref
Capsule	Calcification	No control	Minute shards of calcific detritus commonly abutted on the degenerative areas.	NR	Qual	N/A	[27]
	Collagen content	No control	Capsule tissue is mostly collagenous (range 15.6-88.8% of area; average 57.0% and 70.4% in two different OA groups)	Trichrome	Qual	N/A	[28]
			10.9% of area was stained with Sirius Red in primary TKR patients	Sirius Red	Quant	N/A	[29]
	Type I collagen	↑	Significant increase in collagen I in facet joint capsule (superior and inferior) in OA patients compared to cadaver group	WB	Quant	Yes	[30]
	Type III collagen	=	No statistical difference in collagen III in facet joint capsule (superior and inferior) in OA patients compared to cadaver group	WB	Quant	Yes	[30]
	Collagen cross-links	↑	All OA samples contained reducible cross-links not seen (or in minor quantities) in the joint capsule of healthy adults, namely intermediate Schiff-base cross-links.	IEC	Quant	No	[31]
	Collagen fibre organisation	↓	Disordered compared to control: the normal, smooth, orderly arrangement of collagen fibres is lost and replaced by a jumbled mass like a tangled klein of wool.	EM	Qual	N/A	[32]
	ECM organisation	No control	Matrix appeared pale and more fibrillary and whorled in degenerated than in non-degenerated chondroid areas.	EM, Safranin O-Fast Green	Qual	N/A	[27]
	Elastic fibres	No control	Degenerated areas were more intensely stained than the non-degenerated chondroid areas.	Adehyde-fuchsin	Qual	N/A	[27]
	Elastin	=	No statistical difference in elastin in facet joint capsule (superior and inferior) of OA patients compared to cadaver group	WB	Quant	Yes	[30]
	GAG / proteoglycan	No control	Degenerated areas were less intensely stained with Safrainin O	Safranin O	Qual	N/A	[27]
	GAG: Chondroitin sulphate (CHS)	No control	Chondroitin-6-sulphate (CHS-C) present in joint capsule; major polysaccharide component together with DS and HA. Ratio of CHS-C to DS of approximately 1:1.	ED + F	Quant	N/A	[33]
	GAG: Dermatan sulphate (DS)	No control	Present in joint capsule; major polysaccharide component together with CHS-C and HA. Ratio of CHS to DS of approximately 1:1.	ED + F	Quant	N/A	[33]
	GAG: Hyaluronic acid (HA)	No control	Present in joint capsule. Major polysaccharide component together with CHS-C and DS.	ED + F	Quant	N/A	[33]
	GAG: Hexosamine	No control	~1.1% hexasomine concentration in joint capsule, of which ~80% was glucosamine and ~20% was galactosamine	ED + F	Quant	N/A	[33]

Fat pad	Type I collagen	↓	From ~0.6% in controls to ~0.1% area stained in end-stage OA	Sirius red	Quant	Yes	[34]
	Type III collagen	↓	From ~1.6% in controls to ~0.4% area stained in end-stage OA	Sirius red	Quant	Yes	[34]
	COMP	=	Variable staining, more intense in fibrous than adipose regions of fat pad	IHC, IB	S-quant	Yes	[35]
Intervertebral disc	Calcification	No control	Increasing calcification with increasing OA severity	CT	Quant	N/A	[36]
Ligament	Aggrecan	No control	Weak staining around cells in OA ACL and PCL, only in higher grades of degeneration	IHC	Qual	N/A	[37]
	Calcification	↑	Present in 3-31% of ACL tissue area	not specified	Quant	No	[38]
		No control	Present in 20.7% of ACL samples	H&E	Qual	N/A	[39]
			Present in 25.8% of transverse ligament samples from atlantoaxial OA patients	CT	Qual	N/A	[53]
	Collagen content	=	63.4% (femoral region); 65.1% (midportion); 59.2% (tibial side); reduced collagen occupancy in PCL with increasing degree of OA	TEM; LM	Quant	Yes	[40]
	Type I collagen	↑/=	Collagen I only increased in lateral or medial samples (unclear) in ligamentum flavum in OA compared to cadaver group	WB	Quant	Yes	[30]
		No control	Present throughout most of ECM of ACL and PCL; prevalence similar with different degrees of degeneration	IHC	Qual	N/A	[37]
	Type II collagen	↑	Present in areas of fibrocartilaginous metaplasia in ACL; appears increased	IF	Qual	N/A	[38]
		No control	Focal deposits found around cells in OA ACL and PCL, only present in higher grades of degeneration	IHC	Qual	N/A	[37]
	Type III collagen	=	Tenancy to increase but no significant difference in collagen III in ligamentum flavum (medial and lateral) in OA compared to cadaver group	WB	Quant	Yes	[30]
		No control	Present in ECM surrounding cells in early and advanced degeneration in OA ACL and PCL	IHC	Qual	N/A	[37]
	Collagen fibre density	No control	Mean fibre density in ACL: 142.51/μm^2	TEM	Qual	N/A	[41]
	Collagen fibre diameter	=	84.0nm (femoral region); 81.6nm (midportion); 85.5nm (tibial region). Fibril diameter of PCL smaller in OA patients with marked degeneration (75.1 nm) than those with less marked degeneration (87.5 nm)	TEM	Quant	Yes	[40]
		No control	Fibres most commonly 50-100nm in diameter (0-50nm: 9.0%, 50-100nm: 60.6%, 100-150nm: 19.5%, 150-200nm: 10.8%, >200nm: 0.0%) in ACL	SEM/TEM	Qual	N/A	[41]
	Collagen fibre organisation	↓	Organisation in ACL and PCL decreases with increased OA severity; fibre disorganisation higher in ACL than PCL	H&E + LM	S-quant	Yes	[42]
			Collagen fibre degeneration in PCL positively correlated with severity of OA	Van Gieson and Gomori	S-quant	Yes	[43]
			Collagen fibres in ACL frequently disoriented compared to normal group	H&E + LM	Qual	N/A	[44]
		No control	Disorganised (ACL & PCL)	H&E + LM	Qual	N/A	[45]
			Range from normal to degeneration in >2/3 of tissue (ACL & PCL); ACL more	H&E + LM	S-quant	N/A	[46]

			likely to have significant degeneration (no stats test); positive correlation between ACL appearance and collagen degeneration in PCL				
			Increasingly severe OA associated with reduced collagen organisation at bony insertion of palmar beak ligament	H&E + LM	Qual	N/A	[51]
			Highly variable in ACL and PCL; reduced organisation seen as grade of ligament degeneration increased	H&E + LM	Qual	N/A	[37]
			Most PCLs (65.2%) showed severe collagen fibre degeneration; no correlation between OA grade and fibre degeneration	Gomori trichrome & H&E	S-quant	N/A	[47]
			Dorsoradial ligament: organized collagen bundles with collinear orientation. Anterior oblique ligament: disorganized connective tissue with few collagen fibers, appearance similar to synovial tissue	IF	Qual	N/A	[52]
			Range from parallel to irregular in PCL; organisation decreased with higher OA grades	von Gieson stain + LM	S-quant	N/A	[48]
			Organisation normal in 79% of PCL samples	H&E/Alcian blue + LM	S-quant	N/A	[49]
			Collagen fibres in ACL largely parallel but disordered particularly at bony insertions	Toluidene blue + H&E	Qual	N/A	[41]
			Collagen degeneration was found in all ACL specimen; only few areas of normal collagen were found	H&E	Qual	N/A	[39]
			Disruption of collagen fibre arrangement in PCL, which gets worse with degeneration. Mild: disrupted and wavy, moderate: completely disrupted, severe: almost completely disappeared.	Safranin-O fast-green	Qual	N/A	[50]
	Decorin	No control	Greatest staining in the middle region of the ACL	IHC	Qual	N/A	[41]
	Elastin	↑/=	No significant differences in elastin of ligamentum flavum (medial and lateral) in OA compared to cadaver group	WB	Quant	Yes	[30]
	GAG / proteoglycan	↑	Increased in ACL, especially in areas of cartilaginous metaplasia	Safranin-O	Qual	N/A	[38]
		No control	Present around cells in ACL and PCL	Alcian blue	Qual	N/A	[37]
			Increase in GAG (myxoid change) in 89% of ACL samples	H&E, Masson's Trichrome	Qual	N/A	[39]
Meniscus	Aggrecan	↑	Strong (significant) increase in staining, which was more prominent in the deep zone than the surface zone	IHC	S-quant	Yes	[54]
		No control	Highest density of staining around cell clusters, followed by staining in degenerative areas, and finally staining in intact areas.	IHC	Quant	N/A	[55]
			Found scarcely in meniscus: found in inner meniscus and around cells in middle and outer meniscus.	IHC	Qual	N/A	[56]
	Biglycan	=	No change in fragmentation compared to age-matched controls	WB	Qual	N/A	[57]
	Calcification	↑	Extensive calcified areas; increase in size and frequency compared to control	Alizarin red	Qual	N/A	[58]
			Significant increase in calcification in both medial (11.9% vs 5.2%) and lateral	H&E	Quant	Yes	[59]

			regions (11.1% vs 4.2%), as well as both menisci (11.5% vs 4.7% of surface area)				
			Calcification was seen in almost all OA samples on histology but not in reference. On μCT, calcification of OA samples was more severe (higher volume) and more widespread than reference in both medial and lateral regions. Medial calcification score was higher in OA (3.5 and 3.0) than reference (2.0 and 2.0).	μCT, Safranin-O fast-green	Quant and qual	No	[60]
		↑/=	Increase in lateral anterior and medial anterior regions. Non-significant increase in lateral posterior and non-significant decrease in medial posterior regions.	Von Kossa	S-quant	Yes	[61]
		No control	Heterogeneous distribution, indicating micro-calcifications; contained within both apatite and calcium pyrophosphate crystals in cartilaginous areas	X-ray AS, X-ray F, FTIS	Quant	N/A	[62]
			Calcified areas found	Alizarin red	Qual	N/A	[63]
			Presence of mineral deposition; approximately 80% of mineral areas co-localised with CPPD crystals.	Alizarin Red + Eosin Y	Qual	N/A	[74]
			Calcium deposits found in 16% of OA menisci	IHC	Qual	N/A	[65]
			Increase in calcification in menisci with complete tears vs menisci with no or partial tears	Alizarin Red	Quant	N/A	[66]
			Calcification in all OA menisci, but not the two adults in normal group. Small/medium-sized deposits at the edges of sections (almost all patients); clusters of small-sized deposits inside the meniscus (65% of patients); and widespread medium/large-sized deposits (35% of patients).	Alizarin red	S-quant	Yes	[67]
			4/18 patients had calcification	X-ray	Qual	N/A	[68]
			Extensive meniscal calcification	H&E	Qual	N/A	[69]
			No calcification observed in low or high degeneration groups	H&E	Qual	N/A	[70]
			21/51 medial menisci and 22/51 lateral menisci were positive for calcification (CPPD cyrstals)	Polarised light microscopy	Qual	N/A	[71]
	Cartilage intermediate layer protein (CILP)	↑	CILP was abundant in the matrix separating lacunae of the central region, but undetectable in peripheral regions. Sparse staining in areas of apoptosis and calcification.	IHC	Qual	N/A	[63]
	Collagen content	↑	Significant increase in collagen content compared to control	Colorimetry	Quant	Yes	[72]
		=	No difference in hydroxyproline content (major component of collagen)	Amino acid analyser system	Quant	Yes	[68]
		↓	Statistically significant decrease in staining in OA (grade 0-2) compared to normal (grade 2)	Picrosirius red	S-quant	Yes	[54]
		No control	Significant decrease in collagen content in degenerated vs non-degenerated areas	Colorimetry	Quant	N/A	[73]
			Collagen per dry mass did not show much variation among anterior, central, and posterior regions but varied in the	Spectrophotometry	Quant	N/A	[74]

			radial direction: outer region was higher than other regions. Lower content in medial than lateral meniscus. Collagen per wet mass showed little variation.				
			Collagen content decreased from no to high degeneration; no differences between regions.	IR spectroscopy	S-quant	N/A	[75]
	Collagen cross-links	↑/↓	Significant decrease in mature cross-links pyridinoline and deoxypyridinoline in OA compared to controls. Pentosidine (senescent cross-link) was non-significantly increased.	HPLC	Quant	Yes	[68]
	Type I collagen	↓	Significant decreased throughout meniscus, particularly in the middle zone and deep zones, indicating greater decrease in the middle and deep zones than in the surface zones.	IHC	S-quant	Yes	[54]
		No control	Non-degenerated menisci: staining varied by subject; staining throughout tissue except peripheral vascular area; intense staining in circumferential and radial fibres. Degenerated menisci: staining tended to be absent in severely degenerated menisci.	IHC	Quant	N/A	[76]
			Decrease in staining with increase in damage (no tear > partial tear > complete tear).	IHC	Quant	N/A	[66]
			Staining decreased in menisci that showed degeneration (compared to samples without degeneration), particularly in the body of meniscus using a semi-quantitative score, but not using a quantitative score.	IHC	S-quant / quant	N/A	[77]
			Staining found in middle and outer, but not inner part of meniscus. In the outer meniscus there was more collagen I than collagen II staining (more fibrogenic)	IHC	Qual	N/A	[56]
	Type II collagen	↓	Significant prominent decrease in type II collagen in surface, middle, deep zones.	IHC	S-quant	Yes	[54]
		No control	Highest to lowest staining: anterior, central, and posterior region.	IHC	Quant	N/A	[78]
			Highest density of staining around cell clusters, followed by staining in degenerative areas, and finally staining in intact areas.	IHC	Quant	N/A	[55]
			Non-degenerated menisci: staining similar between subjects; present throughout tissue except peripheral vascular area; intense staining in circumferential and radial fibres. Degenerated menisci: staining increased slightly in mildly degenerative menisci; staining tended to be absent in severely degenerative menisci.	IHC	Quant	N/A	[76]
			Increase in staining with increase in damage (no tear > partial tear > complete tear).	IHC	Quant	N/A	[66]
			Staining found in inner, middle, and outer part of meniscus; collagen II was higher than collagen I in middle meniscus (more chondrogenic)	IHC	Qual	N/A	[56]

	Type III collagen	No control	Non-degenerated menisci: staining similar between subjects; intense staining at exterior peripheral border, on meniscal surface, and along vessels but not in any internal region that expressed collagen II. Degenerated menisci: staining tended to be absent in severely degenerative menisci.	IHC	Quant	N/A	[76]
	Type X collagen	No control	Positive staining in superficial layers	IHC	Qual	N/A	[79]
			High levels throughout the tissue; co-localised with calcium mineral staining	IHC	Qual	N/A	[64]
	Collagen fibre diameter	↓/=	Collagen fibril diameter was decreased and number of fibrils per area was significantly increased in medial menisci, but not in lateral menisci.	TEM	Quant	Yes	[80]
		↓	Decreased diameter in OA compared to control: 35-45 nm in OA compared to 70-80 nm in controls	TEM	Quant	No	[58]
		No control	Average transverse collagen diameter was 95.39 +- 15.87 nm and longitudinal diameter was 96.3 +- 14 nm for control method	TEM	Quant	N/A	[81]
	Collagen fibre organisation	↓/=	Percentage of area occupied by fibrils was reduced in medial but not in lateral menisci.	TEM	Quant	Yes	[80]
		↓	Disorganized collagen fibres in OA; collagen fibres were aligned with a regular pattern of distribution and diameter in controls	TEM	S-quant	No	[58]
			Organised collagen network was lost in medial OA meniscus; medial OA meniscus 24-25 degrees lower orientation angles compared to lateral OA or donor menisci	μCT	Quant	N/A	[82]
			Lateral menisci: fibril bundles tended to be obscure in the surface regions, but were well preserved in the inner area. Medial menisci: less even distribution of fibril bundles; tended to be thicker than controls and were not clearly recognised in the surface regions; obvious wearing and fraying in degenerated areas.	H&E, Masson's trichrome,	Qual	N/A	[80]
			Some separation of individual collagen fibre bundles in patients without a tear; disorganised collagen architecture in patients with a partial tear; collagen architecture completely disorganised.	Safranin O, H&E, Picrosirius red	Qual	N/A	[66]
			Collagen networks were less organised and less compact than the well-organised, parallel-arranged, and compact collagen bundles in normal menisci.	Picrosirius red, H&E	Qual	N/A	[54]
		No control	Collagen fibres were separated and concentrated in the OA meniscus. Also homogenised collagen fibres surrounding cells	H&E	Qual	N/A	[83]
			Fibre angle compared to tidemark remained constant in medial enthesis but increase in lateral enthesis as tissue transitioned from ligament zone to subchondral bone. Significant differences in fibre angle and deviation in calcified fibrocartilage of lateral meniscus.	Picosirius red + PLM	Quant	N/A	[84]

			Tears in collagen fibres found in all studied OA subjects	H&E	Qual	N/A	[85]
			A collection of transverse collagen fibres (transverse ligament) were found running from the synovial edge into the vascular region, which presented a "tree-like" formation of fibres interwoven into the avascular region in all samples	H&E	Qual	N/A	[86]
			Collagen organisation was largely maintained with some circumferential-fibre gapping and fraying in both the central body and horns with age	Confocal microscopy	Qual	N/A	[87]
			Collagen fibre alignment was higher in the low degeneration group (2.18 mean 1/R) than the high degeneration group (1.50 mean 1/R)	Raman spectroscopy	Quant	N/A	[70]
	COMP	No control	Significant decrease in staining: in OA tissue the median staining of ECM was 0 (range 0-1); it was 1 (range 0.66-3) in tissue from meniscal horn tears	IHC	S-quant	Yes	[65]
	Compressive modulus	↓	Instantaneous and equilibrium elastic modulus decreased, particularly in lateral anterior and medial anterior regions	NI	Quant	Yes	[61]
			Aggregate modulus of OA medial menisci was 40% lower than that of control medial menisci, whereas it differed little in lateral menisci	Indentation	Quant	Yes	[80]
		No control	Lateral anterior, lateral posterior, and medial anterior regions showed decreasing instantaneous and equilibrium moduli with increasing degeneration. The medial posterior region had no apparent trend in mechanical properties with degeneration	IRT	Quant	N/A	[88]
	Decorin	↑	Increase in fragmentation compared to age-matched controls	WB	Qual	N/A	[57]
	Fibromodulin	=	No change in fragmentation compared to age-matched controls	WB	Qual	N/A	[57]
	GAG / proteoglycan	↑	Increase in GAG compared to control	Safranin O/fast green	Qual	N/A	[58]
			Intense proteoglycan staining in OA, weak staining in healthy tissue	Safranin O/Fast Green	Qual	N/A	[89]
			Increase in median Safranin-O score throughout the whole meniscus (3 vs 1 in control).	Safranin O	S-quant	Yes	[90]
			Significant increase in proteoglycan content (overall, medial, and lateral) compared to controls; significant increase in medial compared to lateral OA menisci.	Spectrophotometric analysis	Quant	Yes	[72]
			Significantly stronger proteoglycan staining in OA than normal menisci. The increase of safranin-O staining was more prominent in the deep zone than that in the surface zone	Safranin-O Fast green, Alcian Blue, Toluidine Blue	S-quant	Yes	[54]
		No control	Zone 1 (basis to the most peripheral blood vessel): mostly neutral carbohydrates but acid mucopolysaccharide around vessels. Zones 2 & 3 (peripheral blood vessel to the centre in two halves): zone 2 mostly acid mucopolysaccharide; zone 3 mix of neutral carbohydrates and acid	Alcian blue/PAS	S-quant	N/A	[91]

			mucopolysaccharides, with acid mucopolysaccharides in central meniscus, neutral carbohydrates at the top and some edges.				
			Higher proteoglycan staining in anterior 1/3 than central or posterior thirds	Safranin O	Quant	N/A	[78]
			Weak proteoglycan staining in superficial regions	Safranin O	Qual	N/A	[79]
			Specific proteoglycan staining in/around meniscal cell clusters	Safranin O	Qual	N/A	[55]
			42% of OA menisci had none/weak staining.	Alcian blue	S-quant	No	[65]
			Non-degenerated: positive GAG staining on surface of meniscus, vessels, and internal regions where collagen II was found. Degenerated: increase in GAG staining.	IHC	Quant	N/A	[76]
			Proteoglycan score 2.7 ± 0.4 (score 0-3)	Safranin O-Fast Green	S-quant	N/A	[92]
			Little variation in sGAG per dry mass among anterior, central, and posterior regions. Outer and middle regions were higher than inner region. Higher in medial than lateral meniscus. sGAG per wet mass was higher in medial meniscus for the anterior and central regions, but not the posterior region. Content highest to lowest: middle > outer > inner region. Staining confirmed the greatest intensity in middle and lowest inner regions.	DMMB assay / Safranin-O	Quant	N/A	[74]
			Significantly more GAG staining in vascular than avascular areas of meniscus. The inner borders stained more strongly than the other zones.	Toluidine blue	S-quant	N/A	[86]
			Non-significant decrease in proteoglycan content with increasing degeneration; no differences between regions.	IR spectroscopy	Quant	N/A	[75]
	GAG thickness	↑/=	Increased in the lateral anterior, medial anterior and medial posterior regions of calcified zones; no difference in uncalcified zones	Toluidine blue	Quant	Yes	[61]
	GAG: chondroitin sulphate (CHS)	=	CHS-A and CHS-C present. OA menisci showed same composition as those from a comparable age group.	F-UAA-EP	Quant	No	[93]
	GAG: dermatan sulphate (DS)	=	Present. OA menisci showed same composition as those from a comparable age group.	F-UAA-EP	Quant	No	[93]
		No control	Staining present in fibrous matrix of the superficial layer	IHC	Qual	N/A	[94]
	GAG: Hexosamines	No control	Significant increase in hexosamine content in degenerated vs non-degenerated areas	Colorimetry	Quant	N/A	[73]
	GAG: Hyaluronic acid (HA)	=	Present. OA menisci showed same composition as those from a comparable age group.	F-UAA-EP	Quant	No	[93]
		No control	Strong staining in vascular zone, particularly in intima and subintima, in the vicinity of blood vessels and fatty tissue; moderate/weak staining in the inner zones	IHC	S-quant	N/A	[91]
	GAG: heparan sulphate (HS)	=	Present. OA menisci showed same composition as those from a comparable age group.	F-UAA-EP	Quant	No	[93]
	GAG: Keratan sulphate (KS)	=	Present. OA menisci showed same composition as those from a comparable age group.	F-UAA-EP	Quant	No	[93]

	Hydroxyproline	=	No difference in hydroxyproline content	AA analyser system	Quant	Yes	[68]
	Keratocan	=	No change in fragmentation compared to age-matched controls	WB	Qual	N/A	[57]
	Lubricin	↓	Weak staining in OA (moderate staining in outer and middle rim, and weak staining in inner rim), while staining was strong in normal donors in all compartments.	IHC	S-quant	No	[95]
		No control	Staining in all patients, ranging from weak to very strong. Matrix staining strongest directly beneath the surface and decreasing in intensity in deeper tissue. Discrete granular deposits observed. Staining followed crimp and trabecular patterns of collagen fibrils.	IHC	S-quant	N/A	[69]
	Lumican	=	No change in fragmentation compared to age-matched controls	WB	Qual	N/A	[57]
	Viscoelastic properties	↑	Wide distribution of elastic moduli demonstrates stiffer mean values in the outer (364.3 ± 72.2 kPa), middle (401.9 ± 39.2 kPa), and inner regions (365.9 ± 106.5), compared to 303.0 ± 28.3 kPa, 282.4 ± 30.2 kPa, and 274 ± 8.7 kPa, respectively, in aged normal donors	AFM	Quant	No	[89]
		↑/=	Non-significant (p = 0.06) increase in instantaneous modulus in posterior horn (0.17 ± 0.1 MPa vs 0.12 ± 0.07 MPa in control) and entire meniscus (0.17 ± 0.07 MPa vs 0.14 ± 0.08 MPa in control), but significant increase in maximum applied load for both.	Indentation test	Quant	Yes	[90]
		=/↓	Aggregate modulus of OA medial menisci was 40% lower than that of control medial menisci, whereas it differed little in lateral menisci	Indentation	Quant	Yes	[80]
		↓	Instantaneous and equilibrium elastic modulus decreased, particularly in lateral anterior and medial anterior regions	NI	Quant	Yes	[61]
		No control	Lateral anterior, lateral posterior, and medial anterior regions showed decreasing instantaneous and equilibrium moduli with increasing degeneration. The medial posterior region had no apparent trend in mechanical properties with degeneration	IRT	Quant	N/A	[88]
			No significant differences were found between degenerative groups for the tensile modulus. Average tensile modulus: lateral anterior 128.8±62.5 MPa, lateral posterior 119.4±75.6 MPa, medial anterior 112.5±56.6 MPa, and medial posterior 95.9±55.6 MPa. Regardless of degenerative grade or region the average strain at failure was 18.2±5.2%.	Pulling to failure	Quant	N/A	[96]
			Tensile elasticity modulus was 11.66 MPa for control method (cryoprotective preservation). The stress-strain curve revealed a slow-slope curve with a non-abrupt rupture (ductile material). Different results were found for other methods of preservation	Tensile testing machine	Quant	N/A	[96]

			The average values for equilibrium compressive modulus, dynamic compressive modulus, and dynamic shear modulus were 52.2 (39.9, 72.6) kPa, 212.3 (157.8, 282.3) kPa, and 15.5 (12.0, 20.1) kPa, shown as mean (95% upper limit, 95% lower limit) respectively. Overall, mechanical properties exhibited little regional variation.	Torsional rheometer / Microtester	Quant	N/A	[74]
			Equilibrium modulus decreases with increased degeneration (not dependent on region). Hydraulic permeability increased 50% from no to high degeneration, with the anterior being lower than intermedia and posterior regions. Non-significant decrease in tensile modulus from no to high degeneration; no difference between regions.	Compression / tensile test	Quant	N/A	[75]
	Whole ECM composition (proteomics)	↑/=/↓	Differences in medial region, but not in lateral region. Full details in paper.	MS	Quant	Yes	[97]
			Both in- and decreases found in ECM components in OA compared to control. Full details in paper.	MS	Quant	No	[98]
		No control	131 ECM or ECM-associated proteins were identified in meniscal tissue by MatrisomeDB 2.0. COMP, CILP, aggrecan, and 7 collagens were dominantly identified in both lateral and medial menisci. 14 ECM proteins were differentially expressed between medial and lateral meniscus. Full details in paper.	MS	Quant	N/A	[99]
Skeletal muscle	Calcification	No control	Marked calcification of perimysium & juxtavascular tissue of the vastus medialis muscle	H&E + LM	Qual	N/A	[100]
	Collagen content	↑	Collagen content higher in OA vastus lateralis muscle vs controls and negatively correlated with muscle strength	Sirius red	Quant	Yes	[101]
	Type I collagen	↑	Weak to moderate staining of OA vastus lateralis muscles, appears increased compared to control	IHC	S-quant	No	[102]
		No control	All vastus lateralis muscles stained at least weakly positive	IHC	S-quant	N/A	[103]
	Type III collagen	↑	Light to strong staining of OA vastus lateralis muscles, appears increased compared to control	IHC	S-quant	No	[102]
		No control	All vastus lateralis muscles stained at least weakly positive	IHC	S-quant	N/A	[103]
	Type IV collagen	↑	Weak to strong staining in OA vastus lateralis muscles, appears increased compared to control	IHC	S-quant	No	[102]
		No control	All vastus lateralis muscles stained at least weakly positive	IHC	S-quant	N/A	[103]
	GAG / proteoglycan	↑	Increased GAG content in OA vastus lateralis muscle vs control; GAG co-localised with collagen	Wheat germ agglutinin	Quant	Yes	[101]
	Laminin	No control	Present in the basement membrane of OA vastus lateralis muscles	IHC	Qual	N/A	[102]
Synovium	Aggrecan	↑	Staining found in lining and sublining. Increase in staining in sublining and appeared more punctuate in cells in OA	IF	Qual	No	[104]

			while more diffuse within cells in normal).				
	Calcification	↑	Presence of ectopic calcification in OA, but not control samples	H&E	Qual	N/A	[105]
		No control	Calcium deposits found in synovium of nearly all KL-grades, including KL 0	Alicarin red, FITR	Qual	N/A	[106]
			Primary OA: calcification present in subsynovial foci in cases with minimal hyperplasia Rapidly destructive OA: ossification was well defined in the sublining Secondary OA: large areas of calcification were observed.	H&E	Qual	N/A	[121]
			Calcium was found in most OA patients (14/16), mostly located close to the synovial surface; ~1% of the relative volume of the synovium.	IHC (Alizarin red)	S-quant	N/A	[126]
	Collagen content	No control	Found in all OA patients; ~15.37% of the volume of synovium	Movat's pentachrome	S-quant	N/A	[126]
	Type I collagen	↑	Present and increased in sublining; present but unchanged in lining	IF	Qual	N/A	[134]
		No control	Staining found in synoviocytes, their matrix, and the intimal layer of small vessels of the synovium.	IHC	Qual	N/A	[94]
	Type II collagen	No control	Small cartilage particles found in OA synovium	IHC	Qual	N/A	[135]
			Collagen 2-positive fragments surrounded by lining cells of villi in all OA synovial specimens; on average 9.1 fragments (range 3-26) in each x400 magnification field	IHC	S-quant	N/A	[107]
			Cartilaginous fragments of varying sizes entrapped between synovial lining cells.	IHC	S-quant	N/A	[108]
			Cartilage/bone fragments were found in 3 out of 16 samples.	unclear	Qual	N/A	[126]
	Type III collagen	↑	Present in sublining	IF	Qual	N/A	[134]
		No control	Intense nitrated type III collagen staining found in the basement membranes of blood vessels and the lining layer within the fibrous tissue surrounding synoviocytes	IHC	Qual	N/A	[109]
			Staining found in vascular walls and in surrounding connective tissue matrix	IF	Qual	N/A	[136]
	Type IV collagen	↑	Present in sublining	IF	Qual	N/A	[134]
		=	Present in basement membranes of vasculature and pericellular distribution in the intimal layer but not underlying connective tissue. No change compared to trauma control.	IHC	Qual	N/A	[127]
		No control	Present in sublining	IHC	Qual	N/A	[122]
			Present in basement membrane of blood vessels	IF	Qual	N/A	[136]
	Type V collagen	↑	Present in sublining	IF	Qual	N/A	[134]
	Collagen fibre architecture	No control	Accumulation of collagen fibres in early OA; collagen fibres become disordered in late OA.	H&E	Qual	N/A	[110]
			Dense collagen bundles present in sublining; increasingly so with more severe OA. Giant collagen fibrils	EM, LM	Qual	N/A	[132]

			occasionally found in more severely degraded sublining.				
	Collagen cross-links	No control	Pyridinoline (Pyr) and deoxypyridinoline (Dpy) ratio was 14.5+-6.2: Pyr 0.84 mol/mol collagen and Dpy 0.07 mol/mol collagen	LC	Quant	N/A	[111]
			Pyr:Dpr ratio was 25.6	LC	Quant	N/A	[112]
	COMP	No control	Found in and around synovial cells, less staining in sublining	IHC	Qual	N/A	[113]
	Elastin	No control	Intense staining in the internal elastic lamina	IHC	Qual	N/A	[123]
			Elastic fibrils increased in intermediate degeneration	EM, LM	Qual	N/A	[132]
	Fibromodulin	=	Little fibromodulin found in OA synovial tissue. Tenancy towards less staining than control, but not statistically significant	IHC	S-quant	Yes	[133]
	Fibronectin (Fn) (including isoforms)	↑	Highly abundant in areas close to blood vessels or high inflammation	MS & IHC	Quant	No	[114]
			ED-A and ED-B-Fn mainly expressed in the lining; t-FN found throughout the lining and sublining	IHC	Qual	N/A	[115]
			Fn staining found in sublining	IF	Qual	N/A	[134]
		No control	Small amount of Fn staining detected in sublining layer / Fn detected by WB	IHC & IP + WB	Quant	N/A	[137]
			Little Fn staining found in deep sublining	IF	Qual	N/A	[116]
			Weak staining of EDA+ Fn only in proliferative region of OA synovium	IHC	Qual	N/A	[138]
			EDA+ Fn found in OA synovium; most intense staining in the lining layer	IF	Qual	N/A	[117]
			Fn detected in lining, sublining, and blood vessels	IHC	Qual	N/A	[122]
			tFn detected in lining, sublining, and blood vessels; EDA-Fn mainly in linng and vessels, limited staining in the sublining; staining of glycosylated-Fn was similar to EDA-Fn but with reduced intensity; EDB-Fn reduced staining in lining, few vessels stained, limited staining in sublining.	IHC	S-quant	N/A	[139]
			Staining of Fn and EDA-Fn was strong in lining and blood vessels, but weak and irregular in the sublining	IHC	Qual	N/A	[124]
			Fn staining found in lining layer, blood vessels, and area of high collagen content.	IHC	Qual	N/A	[128]
			Fn staining found in lining layer	IHC	Qual	N/A	[118]
			Positive staining for Fn in blood vessels and surrounding matrix.	IF	Qual	N/A	[136]
			Patchy staining on synovial villi and in irregular ECM masses.	IF	Qual	N/A	[129]
	GAG: Chondroitin sulphate (CHS)	↑	CHS-A/C staining increased in interstitial space below the lining layer compared to control. Present in perivascular and highly fibrous regions.	IHC (FCCIS)	Qual	N/A	[119]
		↓	CHS-C absent from the lining layer in OA, while present in normal synovium. Positive staining found in patches of faint staining in sublining, in a narrow band underlying vascular endothelium,	IHC	Qual	N/A	[130]

			and as a diffuse band outlining smooth muscle cells of the tunica media in larger vessels.				
	GAG: Dermatan sulphate (DS)	↑	Increased in interstitial space below the lining layer compared to control. Present in perivascular regions (in and around vascular endothelial cells) and subsurface interstitial space.	IHC (FCCIS)	Qual	N/A	[119]
		=	Distributed through superficial and deep matrix; faint condensation in the adventitia. No differences with normal synovium reported.	IHC	Qual	N/A	[130]
		No control	Staining found in synoviocytes and their surrounding matrix at the adventitial layer of small blood vessels	IHC	Qual	N/A	[94]
	GAG: Hyaluronic acid (HA)	↑	HA found in blood vessels (at times extending into surrounding matrix), in areas of infiltrating cells, and reticular staining in the lining, which decreased upon hyperplasia. Low-to-moderate staining in OA compared to faint staining in normal tissue.	IHC	Qual	N/A	[144]
		=	HA mainly found in lining, content varied strongly between patients; mean content (249 +- 34.8 μg/g) not significantly different from control (227.7 +- 35.4 μg/g).	IHC + SPA	Quant	Yes	[140]
		No control	Staining was weak and restricted to the lining layer.	IHC	S-quant	N/A	[122]
			Present in perivascular regions.	IHC (FCCIS)	Qual	N/A	[119]
	GAG: Heparin sulphate (HS)	↑	HS increased in interstitial space below the lining layer compared to control. Present on and around vascular endothelial cells.	IHC (FCCIS)	Qual	N/A	[119]
		No control	HS was detected with a diffuse pattern involving all vessels in OA sections	IF	Qual	N/A	[141]
	Laminins	↑	EHS laminin (laminin-111) staining strongest in lining, areas of the sublining, and blood vessel basement membranes; occasional weaker staining in stromal pericellular areas. Moderate to strong staining for a5 and b1 (mainly in blood vessels but also in lining and sublining) and b2 laminin, which stained more extensively but less so in blood vessels.	IHC	S-quant	No	[125]
		=	a2 and a3 laminin showed no/weak staining. No changed compared to trauma control.	IHC	S-quant	No	[125]
			a4 laminin showed weak staining in lining, strong staining in vascular basement membranes.	IF	Qual	N/A	[142]
			EHS-laminin staining in basement membrane of vasculature and pericellular in intimal layer.	IHC	Qual	N/A	[127]
			Laminin (unspecified) present in vascular basement membranes and areas of sublining with early connective tissue proliferation but not in mature fibrous tissue.	IF	Qual	N/A	[136]
		↓	Weak a5 laminin staining in lining, strong staining in vascular basement membranes.	IF	Qual	N/A	[142]

		No control	Pericellular distribution in the synovial lining layer. Staining appears to decrease in cases of severe inflammation	IHC	S-quant	N/A	[131]
	Latent TGF-β-binding protein 1 (LTBP-1)	↑	Increased staining (IHC); 2-fold increase in abundance (WB).	IHC, WB	Quant	Yes	[120]
	Lumican	=	High levels throughout synovial and subsynovial tissue	IHC	S-quant	NR	[133]
	Reticulin	No control	Found in vascular walls and in surrounding connective tissue matrix	IF	Qual	N/A	[136]
	Vitronectin	No control	Found in the lining layer and some staining is present in the sublining often in fibril like structures.	IHC	Qual	N/A	[118]
	Whole ECM composition (proteomics)	No control	Several ECM proteins were found. Several, including collagen 2 alpha1, versican, and cartilage intermediate layer protein 1), were higher in OA than RA.	LC-MS/MS	Quant	N/A	[143]
Tendon	Calcification	↑	Increase in internal obturator tendon calcification in OA compared to control	Von Kossa	S-quant	Yes	[145]
		= / ↓	Lower percentage of calcification in OA biceps but no difference in subscapularis tendon	Von Kossa + LM	S-quant	Yes	[146]
		No control	Mean calcification score in OA Achilles tendon 2.79 (scored 0-6 for both tendons: 0=none, 1 = <5mm, 2 = 5-10mm, 3 = ossification >10mm)	Ultrasound	S-quant	N/A	[147]
	Type I collagen	=	Present in all OA long head of biceps tendons	IHC	S-quant	Yes	[148]
	Type III collagen	=	Present in all OA long head of biceps tendons	IHC	S-quant	Yes	[148]
	Collagen fibre diameter	↑	Relatively fewer small and medium sized fibres (<30 & 31-60 nm) in OA internal obturator tendon vs control	TEM	Quant	Yes	[145]
		↑ / =	Increase in biceps (66.1nm vs 59.0nm in control); no changes in subscapularis (55.3nm vs 54.0nm in control)	H&E + LM, TEM	Quant	Yes	[146]
		=	Mean diameter 68.3nm for in OA gluteus medius tendon (vs 67.6nm in control)	TEM	Quant	Yes	[149]
	Collagen fibre organisation	=	Distal portion of long head of biceps tendon has more organised collagen than proximal; no difference with control	Polarised light	Quant	Yes	[148]
		↓	Irregular collagen structure more common in OA biceps and subscapularis tendon vs control	TEM	S-quant	Yes	[146]
			Slightly higher disorganisation of fibre structure in OA gluteus medius tendon than control	H&E + Alcian blue/PAS	S-quant	No	[149]
			Irregular patterns (in ultrastructure) of collagen fibrils in OA internal obturator tendon compared to control	H&E + LM, TEM	Quant	Yes	[145]
	Decorin	=	Present in all OA long head of biceps tendons	IHC	S-quant	Yes	[148]
	GAG / proteoglycan	↑	Greater proteoglycan content in OA long head of biceps tendon than control; greater proteoglycan content in proximal compared to distal tendon	Alcian blue	Quant	Yes	[148]
			Increase in GAG between collagen fibrils in OA internal obturator tendon	Alcian blue	Quant	Yes	[145]

		=	No difference in GAG in OA biceps and subscapularis tendon compared to control	Alcian blue	S-quant	Yes	[146]
		↓	Slight decrease in average GAG score in OA gluteus medius tendon compared to control	Alcian blue/PAS	S-quant	No	[149]

AA, amino acid; ACL, anterior cruciate ligament; CILP, cartilage intermediate layer protein; CHS, chondroitin sulphate; CPPD, calcium pyrophosphate deposition; DS, dermatan sulphate; ECM, extracellular matrix; EDA, ethylenediamine; ED + F, enzymatic digestion and fractionation; EM, electron microscopy; FCCIS, fine cationic colloidal iron staining; FITR, Fourier-transformed infrared spectroscopy; Fn, fibronectin; F-UAA-EP, fractination - uronic acid assay – electrophoresis; GAG, glycosaminoglycan; HA, hyaluronic acid; H&E, haematoxylin and eosin; HS, heparan sulphate; IB, immunoblotting; IEC, ion exchange chromatography; IHC, immunohistochemistry; IP, immunoprecipitation; IRT, indentation relaxation tests; KL-grade, Kellgren-Lawrence grade; LC, liquid chromatography; LM, light microscopy; N/A, not applicable; NI, nanoindentation; NR, not reported; OA, osteoarthritis; PAS, periodic acid Schiff; PCL, posterior cruciate ligament; PLM, polarized light microscopy; qual, qualitative; quant, quantitative; s-quant, semi-quantitative; SPA, sandwich-binding protein assay; TEM, transmission electron microscopy; WB, western blot.

Table ii. Structural extracellular matrix composition and architecture in animal models of osteoarthritis. The studied joint in all studies is the stifle joint.

Tissue	ECM feature	Change vs control	Species (strain)	Model	Description of feature in OA tissue	Measurement technique(s)	Analysis	Stat. test	Ref
Capsule	Collagen III	=	Mouse (C57BL/6)	DMM	Diffuse staining; present in vascular endothelium	IHC	Qual	No	[150]
Ligament	Calcification / mineralisation	↑	Mouse (CBA, STR/ort)	STR/ort	Areas of bone formation in the collateral ligaments of STR/ort mice, which were more significant in severe OA	Toluidine blue	Qual	No	[151]
			Mouse (CBA, STR/ort)	STR/ort	Calcification more common in MCLs and LCLs of OA mice vs control; MCL calcification positively correlated and LCL mineralisation was negatively correlated with OA progression	X-ray	S-quant	Yes	[152]
	Collagen content	↓	Rabbit (NZW)	ACLT	Lower intensity in peaks may indicate a reduction in collagen in MCL/LCL in OA	Raman Spectroscopy	Quant	No	[154]
	Type II collagen	↑	Mouse (CBA, STR/ort)	STR/ort	Collateral ligaments: collagen 2 deposition in OA mice, but not in controls. ACL: collagen 2 deposition at the insertion site, while none was observed in controls.	Toluidine blue	Qual	No	[151]
	Type III collagen	=	Mouse (C57BL/6)	DMM	Diffuse staining in ligaments of the hind limb; present in vascular endothelium	IHC	Qual	No	[150]
	Collagen cross-links	↑/=	Mouse (STR/ort)	SRT/ort	Increased immature cross-links in ACL of young OA mice vs young control (22-30 weeks), but no difference in ACL of old OA mice vs old control; higher in ACL of young OA mice than old OA mice.	Cellulose chromatography, AA analysis	Quant	Yes	[153]
	Collagen fibre diameter	See text	Sheep (Suffolk cross)	ACL + MCL transection	Modal collagen fibril diameter 48-96nm in LCL & PCL. OA PCLs had fewer medium size fibrils (96-192nm) than control ligaments	TEM	Yes	Yes	[156]
	Collagen fibre organisation	↓	Sheep (Suffolk cross)	Partial ACLT	Decrease in collagen fibre organisation in PCL in OA compared to control	H&E	S-quant	Yes	[157]
			Rabbit (NZW)	ACLT	Decrease in collagen fibre organisation in MCL in OA compared to control	Ultrasound	S-quant	Yes	[155]
	GAG / Proteoglycan	↑	Mouse (CBA, STR/ort)	STR/ort	Collateral ligaments: increase in staining in in OA compared to control. ACL: Increase in staining in OA ACL (grade 2 or higher), which expanded through the entire ACL in severe OA, while only weak staining was seen in control mice.	Toluidine blue	Qual	No	[151]

		↓	Rabbit (NZW)	ACLT	Lower intensity in peaks may indicate a reduction in GAG in MCL/LCL in OA	Raman Spectroscopy	Quant	No	[154]
	Mechanical strength	↓	Mouse (STR/ort)	STR/ort	Lower ultimate strength in ACL in OA compared to control	Tensile strength machine	Quant	Yes	[153]
Meniscus	Calcification / mineralisation	↑	Mouse (C57BL/6)	Mechanical loading	Increase in ectopic mineralisation	μCT	Quant	No	[158]
			Mouse (C57Bl/6J)	DMM	At 8 weeks, significant increase in meniscal ossicle formation	nanoCT	Quant	Yes	[159]
			Mouse (C57BL/6J)	Aged	Increase in mineralisation in female and male menisci (lateral/medial, anterior/posterior) in aged mice (27m) compared to young mice (3m)	μCT	Quant	Yes	[160]
			Mouse (CBA, STR/ort)	STR/ort	Ossification in fibrous region of meniscus in OA	Toluidine blue	Qual	No	[151]
		↑/=	Rabbit (NZW)	ACLT	Calcification detected in torn OA menisci, but not in non-altered regions of OA menisci or normal menisci.	Alizarin Red	Qual	No	[162]
	Type I collagen	↑	Rabbit (NZW)	ACLT	At 3 and 8 weeks, staining intensity increased in the outer region adjacent to the fissure medially and increased throughout the tissue laterally.	IHC	Qual	No	[163]
	Type II collagen	↑	Mouse (BALB/cByJ)	DMM	Abnormal staining (in vascular region associated with hypertrophic changes)	IHC	Qual	No	[161]
			Mouse (CBA, STR/ort)	STR/ort	Staining in the fibrous region, particularly in areas surrounding bone formation and in the outer areas near the capsular attachment site, while it was only detected at cartilage surfaces of the meniscus in controls.	IHC	Qual	No	[151]
		↑/=	Rabbit (NZW)	ACLT	At 3 and 8 weeks, staining intensity increased in the outer region adjacent to the fissure and in inner medial meniscus and was not significantly altered laterally.	IHC	Qual	No	[163]
	Type III collagen	↑	Rabbit (NZW)	ACLT	At 3 and 8 weeks, staining intensity increased in the outer region adjacent to the fissure medially and staining was increased throughout the tissue laterally.	IHC	Qual	No	[163]
		=	Mouse (C57BL/6)	DMM	In OA and control mice, staining was found in pericellular distribution and in vascular endothelium	IHC	Qual	No	[150]
	Type X collagen	↑/=	Rabbit (NZW)	ACLT	Detected in torn OA menisci, but not in non-altered regions of OA menisci or normal menisci.	IHC	Qual	No	[162]
	Collagen fibre diameter	↑	Rabbit (Chinese)	Cartilage injury	Collagen thickening present in animals after 1-2 weeks	H&E	Qual	No	[164]
	Collagen fibre organisation	=/↓	Rabbit (NZW)	ACLT	Tie fibre organisation decreased: non-significant increase in tie fibre organisation score in the anterior, and significant increase in posterior region	Biphotonic confocal imaging	S-quant	Yes	[165]
		↓			Disorganisation seen at 3 weeks, not seen in control	H&E	Qual	No	[163]

					OA menisci displayed less compact collagen bundles, with undulated fibres in both regions, while bundles in healthy menisci were made of straight fibres aligned in the circumferential direction in both regions.	Biphotonic confocal imaging	Qual	No	[165]
					OA menisci had less compact bundles with undulated fibres in both regions compared to healthy menisci, which had compact collagen bundles made of straight fibres aligned in circumferential direction	Biphotonic confocal imaging	Qual	No	[166]
					Tie fibre organisation decreased: increase in tie fibre organisation score in both anterior and posterior region.	Biphotonic confocal imaging	S-quant	No	[166]
			Rabbit (Chinese)	Cartilage injury	At 6 weeks, collagen fibres are disordered in OA, while they are ordered in healthy menisci	H&E	Qual	No	[164]
	Fibromodulin	=	Mouse (C57BL/6)	DMM	Minimal presence in meniscus, no differences noted	IHC	Qual	No	[150]
	Proteoglycan / GAG content	↑	Mouse (CBA, STR/ort)	STR/ort	Increase in proteoglycan content	Toluidine blue	Qual	No	[151]
		=/↓	Rabbit (NZW)	ACLT	Significant decrease in staining medially after 3 weeks, no significant changes laterally	Safranin O	Qual	No	[163]
					Significant decrease in GAG coverage in anterior; non-significant increase in posterior region.	Safranin O/Fast Green	S-quant	Yes	[165]
					Significant decrease in GAG coverage in anterior meniscus, but no significant differences in posterior region.	Safranin O/Fast Green	S-quant	Yes	[166]
		↓	Pig (Yucutan minipig)	DMM	Anterior horn: significant decrease in proteoglycan ratio 1 and 3 months after DMM. Posterior horn: small decrease after 1 month and significant decrease after 3 months.	Safranin O/Fast Green	Quant	Yes	[168]
					Significant decrease in proteoglycan staining at 1*, 3*, and 6 months after DMM injury in both the anterior and posterior horn compared to sham.	Safranin O-Fast Green	Quant	Yes	[169]
			Rat (Wistar)	ACLT	Slight loss of Safranin O staining	Safranin O	Qual	No	[167]
	Viscoelastic properties	=	Pig (Yucutan minipig)	DMM	No change in linear modulus 1, 3, or 6 months after DMM	Tensile testing	Quant	Yes	[169]
					No change in toe-region modulus 1, 3, or 6 months after DMM	Tensile testing	Quant	Yes	[169]
			Rabbit (NZW)	ACLT	Instantaneous modulus decreased in both anterior and posterior regions, but no significant differences.	IRT	Quant	Yes	[166]
		=/↓			Instantaneous modulus decreased significantly in the anterior region (2.9MPa for healthy, 1.3MPa for OA). Non-significant decrease (1.5x) in posterior. Anterior was stiffer than posterior region in health and disease.	IRT	Quant	Yes	[165]

					Elastic fraction was unaffected in anterior, but significantly decreased in posterior region. No significant differences between anterior and posterior regions.	IRT	Quant	Yes	[165]
					Equilibrium modulus was significantly decreased in anterior region (0.6MPa for healthy, 0.26MPa for OA), non-significant decrease in posterior region.	IRT	Quant	Yes	[166]
					Elastic fraction was significantly lower in posterior region (0.21MPa for healthy, 0.16MPa for OA); no differences in anterior region.	IRT	Quant	Yes	[166]
		↓			Equilibrium modulus significantly decreased in anterior (57%; 0.6MPa in healthy, 0.14 MPA in OA) and posterior regions (45%: 0.14MPa in healthy, 0.099MPa in OA)	IRT	Quant	Yes	[165]
			Pig (Yucutan minipig)	DMM	Significant decrease in transition strain 6 months, but not 1 or 3 months, after DMM compared to control	Tensile testing	Quant	Yes	[169]
Skeletal muscle	Collagen content	↓	Rat (Sprague-Dawley)	MIA	Decrease in collagen levels on day 56 and 87 compared to naïve group	ELISA	Quant	Yes	[171]
	Viscoelastic properties	↑	Rabbit (NZW)	Adapted Videman method	Elastic modulus increased vs control in biceps femoris & rectus femoris	Micro-force tension-torsion	Quant	Yes	[170]
Synovium	Aggrecan	=	Rat (unspecified)	DMM	Staining found in the lining and sub-lining layer. Staining was more punctuate in cells in OA, while it was more diffuse throughout the cell in normal synovium.	IF	Qual	No	[104]
	Calcification	↑	Mouse (C57BL/6)	Mechanical loading	Ectopic mineralisation	3D μCT	Quant	No	[158]
	Collagen content	↑	Rat (albino)	Cartilage defect	Significant increase in the mean area covered by collagen fibres in the subintimal stroma	Mallory stain	Quant	Yes	[173]
			Rabbit (domestic)	Modified Hulth method	Significant increase in collagen volume fraction in rabbits 4 and 12 weeks after OA induction compared to 12 weeks sham control.	Masson's trichrome	S-quant	Yes	[185]
			Rat (Sprague-Dawley)	MIA	Marked increase in collagen content compared to control	Sirius red	Qual	No	[174]
					Marked increased collagen deposition	Sirius red	Qual	No	[175]
					Increase in collagen deposition	Masson's, Sirius red	Qual	No	[176]
					Significant increase in blue collagen staining (% fibrosis area) at 2, 4, and 8 weeks in IFP/synovium	Masson's trichrome	Quant	Yes	[177]
				ACLT	Significant increase in collagen staining	Sirius red	S-quant	Yes	[178]
				ACLT, DMM, MIA	Significant increase in amount of Sirius red positive staining and Masson's positive areas in all 3 OA models compared to control on day 14 and 28 after OA induction	Sirius red, Masson's trichrome	S-quant	Yes	[179]

	Type I collagen	↑	Rabbit (domestic)	Modified Hulth method	Significant increase in collagen 1 immunofluorescence in rabbits 4 and 12 weeks after OA induction compared to 12 weeks sham control.	IF	S-quant	Yes	[185]
			Rat (Sprague-Dawley)	MIA	Increased collagen 1 deposition (Sirius red); significant increase in COL1A1 abundance (WB)	Sirius red, WB	Qual, S-quant	No, Yes	[180]
					Significant increase in collagen 1 relative protein level	WB	S-quant	Yes	[174]
					Significant increase in the percentage of collagen I-positive areas	IHC	S-quant	Yes	[175]
				ACLT, DMM, MIA	Significant increase in amount of collagen 1 staining in all 3 OA models compared to control on day 14 and 28 after OA induction	IHC	S-quant	Yes	[179]
	Type III collagen	=	Mouse (C57BL/6)	DMM	Diffuse pattern staining; present in vascular endothelium	IHC	Qual	No	[150]
	Type V Collagen	↑	Mouse (C57BL/6J)	DMM	Significant increase in area positive for collagen 5a1	IHC	Quant	Yes	[172]
	Type XIV Collagen	↑	Mouse (C57BL/6J)	DMM	Significant increase in area positive for collagen 14a1	IHC	Quant	Yes	[172]
	Collagen fibre diameter	↑	Rat (Wistar albino)	Mx	Thick collagen fibres in the lining and sublining and around the blood vessel, compared to thin fibres in controls. Strong PAS reaction present, which demonstrates the presence of glycogen and mucoproteins.	H&E, Alcian blue w/ PAS	Qual	No	[181]
		=	Rat (Sprague-Dawley)	ACLT	In all groups: minimum= 133+-10.27 nm; maximum = 133.62+-21.03 nm.	AFM	Quant	Yes	[182]
	Collagen fibre organisation	=	Rat (Sprague-Dawley)	ACLT	No significant difference between the maximum and minimum D-periodic banding in all groups (68.19±12.73 nm *vs* 65.43±2.57 nm)	AFM	Quant	Yes	[182]
		↓	Rat (Sprague-Dawley)	ACLT	Fibre alignment more disordered vs control in both anterior and posterior capsule	AFM	Qual	No	[182]
			Rabbit (Flanders Giant)	Vitamin A injection	Decrease in collagen fibre arrangement over-time after OA induction: no change after 3 days, collagen fibres were closely packed and showed areas of calcium-like deposits after 6 days, and they were numerous and intermingled with electron transparent areas after 9 days	EM, Toluidine blue	Qual	No	[186]
	COMP	↑/↓	Rats (Wistar)	MIA	Increase in COMP level day 2 after MIA injection (but no increase on days 7, 21, 28)	WB	S-quant	Yes	[183]
	Fibromodulin	=	Mouse (C57BL/6)	DMM	Variable immunopositivity, no differences noted	IHC	Qual	No	[150]
	Lubricin	↓	Rat (Wistar)	ACLT	Decrease in lubricin immunolabelling (moderate in OA vs strong in control).	IHC	S-quant	Yes	[184]

	Viscoelastic properties	↓	Rat (Sprague-Dawley)	ACLT	Elastic modulus increased with severity of OA (time post-surgery) and was higher in the anterior than posterior capsule	AFM	Quant	Yes	[182]
Tendon	Calcification	↑	Rat (Sprague-Dawley)	ACLT	Calcification began inferior to mid-section of patella and progressed to ossification. Calcification more common in OA than control	μCT	Qual	No	[187]

AA, amino acid; ACL, anterior cruciate ligament; ACLT, anterior cruciate ligament transection; AFM, atomic force microscopy; DMM, destabilization of the medial meniscus; ECM, extracellular matrix; EM, electron microscopy; GAG, glycosaminoglycan; H&E, haematoxylin and eosin; IHC, immunohistochemistry; IRT, indentation relaxation tests; LCL, lateral cruciate ligament; MCL, medial cruciate ligament; MIA, monoiodoacetate; Mx, meniscectomy; N/A, not applicable; NR, not reported; NZW, New Zealand white; OA, osteoarthritis; PAS, periodic acid Schiff; PCL, posterior cruciate ligament; qual, qualitative; quant, quantitative; s-quant, semi-quantitative; WB, western blot.

*Data from 1 and 3 months was previously published in Bansal et al (2020) [166]

Table iii. 2015 Office of Health Assessment and Translation (OHAT) risk of bias analysis of all included studies. Bias in each category is rated according to the following four-point scale: ++, definitely low risk of bias; +, probably low risk of bias; -, probably high risk of bias; --, definitely high risk of bias. Questions 1 to 6 only apply to certain study types. Of note, several studies on human osteoarthritis did not recruit a healthy control group, but instead performed subgroup analysis of a single cohort. In these cases, confounding bias was assessed in question 11.

Domains	**SB**			**CB**	**PB**		**A/EB**	**DB**		**SRB**	**OB**
OHAT questions	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Abdul Sahib (2017)	N/A	N/A	-	-	N/A	N/A	+	-	--	-	++
Abraham (2014)	N/A	N/A	-	-	N/A	N/A	++	-	+	++	++
Akisue (2002)	N/A	N/A	-	-	N/A	N/A	++	++	+	++	++
Allain (2001)	N/A	N/A	N/A	N/A	N/A	N/A	++	-	-	++	-
Almasry (2015)	+	-	N/A	N/A	--	-	-	++	+	++	++
Anderson-Mackenzie (1999)	N/A	N/A	++	++	N/A	N/A	-	++	+	++	++
Bansal (2020)	-	-	N/A	N/A	+	-	-	++	++	++	++
Bansal (2021)	+	-	N/A	N/A	+	-	-	++	++	++	++
Barton (2021)	-	-	N/A	N/A	-	-	-	+	++	+	++
Battistelli (2019)	N/A	N/A	-	-	N/A	N/A	-	++	-	--	--
Bedingfield (2021)	--	--	N/A	N/A	--	--	-	++	+	++	++
Belluzzi (2020)	N/A	N/A	++	++	N/A	N/A	-	-	+	++	++
Bryk (2021)	-	-	N/A	N/A	-	-	-	+	+	-	++
Cameron (1973)	N/A	N/A	-	-	N/A	N/A	+	-	-	-	-
Campbell (2015)	N/A	N/A	++	++	N/A	N/A	-	++	+	++	++
Castrogiovanni (2019)	-	-	N/A	N/A	-	-	-	++	++	++	++
Catheline (2021)	-	-	N/A	N/A	+	-	-	++	++	++	++
Chang (2005)	N/A	N/A	-	-	N/A	N/A	-	-	+	++	++
Cheng (1996)	N/A	N/A	--	++	N/A	N/A	++	++	++	++	++
Christensen (2019)	N/A	N/A	--	--	N/A	N/A	+	+	-	++	++
Cillero-Pastor (2015)	N/A	N/A	-	-	N/A	N/A	+	-	+	++	++
Cui (2023)	-	-	N/A	N/A	--	-	-	+	+	++	++
Cutolo (1992)	N/A	N/A	-	-	N/A	N/A	+	++	-	-	-
Dai (2020)	+	-	N/A	N/A	++	-	+	++	+	++	++
Dessombz (2013)	N/A	N/A	N/A	N/A	N/A	N/A	--	++	+	+	++
DiCesare (1999)	N/A	N/A	-	-	N/A	N/A	+	-	+	+	++
DiFrancesco (1995)	N/A	N/A	+	+	N/A	N/A	++	-	-	-	+
Dijkgraaf (1997)	N/A	N/A	-	+	N/A	N/A	-	++	-	++	-
Doerschuk (1999)	N/A	N/A	-	-	N/A	N/A	-	++	-	+	++
Ea (2013)	N/A	N/A	-	-	N/A	N/A	+	++	++	++	-

Endo (2018)	+	-	N/A	N/A	+	-	-	++	-	+	++
Ene (2015)	N/A	N/A	-	-	N/A	N/A	+	+	-	--	++
Exposito Molinero (2016)	N/A	N/A	+	+	N/A	N/A	+	-	+	++	++
Fan (2012)	N/A	N/A	+	+	N/A	N/A	++	++	-	-	++
Fink (2007)	N/A	N/A	N/A	N/A	N/A	N/A	+	++	-	++	++
Fischenich (2015)	N/A	N/A	-	-	N/A	N/A	-	-	++	++	++
Folkesson (2020)	N/A	N/A	++	++	N/A	N/A	++	++	+	++	++
Fuhrmann (2015)	N/A	N/A	+	+	N/A	N/A	++	-	++	++	-
Funakoshi (2007)	-	-	N/A	N/A	-	-	+	++	+	++	++
Gamal (2019)	-	-	N/A	N/A	-	-	+	+	-	++	++
Ghosh (1975)	N/A	N/A	-	-	N/A	N/A	-	+	+	-	++
Gouldin (2023)	N/A	N/A	++	++	N/A	N/A	++	+	++	++	++
Grevenstein (2020)	N/A	N/A	-	-	N/A	N/A	++	-	-	++	++
Haut Donahue (2021)	N/A	N/A	++	++	N/A	N/A	+	-	+	++	++
Heinegård (1968)	N/A	N/A	-	-	N/A	N/A	++	+	+	++	--
Hellberg (2023)	N/A	N/A	-	-	N/A	N/A	++	+	-	++	-
LeGraverand (2001) (ref [163])	-	-	N/A	N/A	-	-	-	+	+	++	++
LeGraverand (2001) (ref [162])	-	-	N/A	N/A	-	-	-	+	-	++	++
Herbert (1973)	N/A	N/A	-	-	N/A	N/A	++	-	+	++	--
Hino (1995)	N/A	N/A	-	-	N/A	N/A	+	+	-	--	+
Hino (2020)	N/A	N/A	N/A	N/A	N/A	N/A	+	-	++	++	++
Ibrahim (2019)	N/A	N/A	++	++	N/A	N/A	+	+	+	++	++
Ibrahim (2021)	N/A	N/A	+	+	N/A	N/A	-	-	++	++	++
Ishizuka (2016)	N/A	N/A	--	--	N/A	N/A	--	++	-	++	-
Itokazu (1998)	N/A	N/A	-	-	N/A	N/A	++	-	--	++	--
Jacquet (2018)	N/A	N/A	N/A	N/A	N/A	N/A	+	++	++	++	++
Jacquet (2019)	N/A	N/A	N/A	N/A	N/A	N/A	+	++	+	++	++
Johnson (2001)	N/A	N/A	-	-	N/A	N/A	-	-	-	++	-
Karjalainen (2021)	N/A	N/A	--	++	N/A	N/A	++	++	+	++	++
Karube (1981)	N/A	N/A	-	-	N/A	N/A	++	-	+	++	-
Katsuragawa (2010)	N/A	N/A	+	+	N/A	N/A	-	++	-	++	++
Kaufmann (2003)	N/A	N/A	--	--	N/A	N/A	++	+	+	++	--
Kiraly (2017)	N/A	N/A	N/A	N/A	N/A	N/A	+	-	-	-	++
Klareskog (1986)	N/A	N/A	-	-	N/A	N/A	+	-	-	-	++
Kodama (2018)	N/A	N/A	N/A	N/A	N/A	N/A	--	++	-	++	++
Komro (2020)	N/A	N/A	--	--	N/A	N/A	+	++	+	++	+
Konttinen (1999)	N/A	N/A	-	-	N/A	N/A	++	-	-	++	-
Konttinen (2001)	N/A	N/A	+	+	N/A	N/A	-	-	+	++	++
Kragstrup (2019)	N/A	N/A	N/A	N/A	N/A	N/A	+	++	+	++	++

Krawetz (2022)	-	-	-	-	-	--	++	++	-	++	++
Kriegsmann (2004)	N/A	N/A	-	-	N/A	N/A	+	-	+	-	-
Kumagai (2012)	N/A	N/A	N/A	N/A	N/A	N/A	+	++	+	++	-
Kwok (2014)	N/A	N/A	-	-	N/A	N/A	++	++	-	++	-
Lapadula (1995)	+	-	N/A	N/A	-	-	+	-	-	-	--
Lee (2020)	-	-	N/A	N/A	-	-	-	+	-	-	++
Lee (2021)	+	-	N/A	N/A	+	++	-	+	+	++	++
Levillain (2017) (ref [165])	-	-	N/A	N/A	-	-	++	++	-	++	++
Levillain (2017) (ref [166])	+	-	N/A	N/A	-	-	-	++	-	++	++
Levy (2013)	N/A	N/A	N/A	N/A	N/A	N/A	-	+	++	++	-
Li (2000)	N/A	N/A	-	-	N/A	N/A	+	-	-	++	-
Li (2020)	+	-	N/A	N/A	+	-	-	+	+	++	++
Li (2021)	++	-	N/A	N/A	++	-	+	+	-	+	++
Limberg (2022)	N/A	N/A	++	++	N/A	N/A	++	+	++	++	++
Loeser (2013)	+	-	N/A	N/A	++	-	+	++	+	++	++
Lopez-Franco (2016)	N/A	N/A	-	-	N/A	N/A	++	+	++	++	++
Mapp (1985)	N/A	N/A	-	-	N/A	N/A	+	-	+	++	-
Marczak (2017)	N/A	N/A	++	++	N/A	N/A	++	++	-	++	++
Martins (2018)	N/A	N/A	-	-	N/A	N/A	++	++	+	++	++
Masuda (1991)	N/A	N/A	+	+	N/A	N/A	+	--	-	++	-
Mattiello-Svetzut (2013)	N/A	N/A	N/A	N/A	N/A	N/A	--	++	++	++	++
Mazzocca (2013)	N/A	N/A	+	+	N/A	N/A	--	+	++	++	++
McDaniel (2017)	N/A	N/A	++	++	N/A	N/A	+	++	-	++	++
McErlain (2008)	+	-	N/A	N/A	++	-	++	++	-	++	++
Meknas (2012)	N/A	N/A	-	-	N/A	N/A	+	-	+	++	++
Melrose (2008)	N/A	N/A	++	++	N/A	N/A	-	-	-	++	-
Miller (2014)	-	++	N/A	N/A	++	++	++	-	++	++	--
Mine (2013)	N/A	N/A	-	-	N/A	N/A	-	-	-	++	-
Mobargha (2014)	N/A	N/A	N/A	N/A	N/A	N/A	+	++	-	++	++
Monibi (2021)	N/A	N/A	-	-	N/A	N/A	-	-	++	+	++
Muschter (2020)	-	-	N/A	N/A	++	-	--	++	++	++	++
Musumeci (2014)	N/A	N/A	+	+	N/A	N/A	+	++	++	++	++
Nagata (2000)	N/A	N/A	-	-	N/A	N/A	++	++	-	++	-
Nakahara (2013)	N/A	N/A	+	+	N/A	N/A	--	++	-	--	+
Nakamura (2022)	N/A	N/A	N/A	N/A	N/A	N/A	++	+	--	++	++
Nakashima (1998)	N/A	N/A	N/A	N/A	N/A	N/A	++	++	-	++	++
Nelissen (2001)	N/A	N/A	-	-	N/A	N/A	++	++	-	++	-
Nikkari (1995)	N/A	N/A	-	-	N/A	N/A	++	-	-	++	-
Nishida (1995)	N/A	N/A	-	-	N/A	N/A	+	-	-	++	-
Noehren (2018)	N/A	N/A	+	+	N/A	N/A	-	++	++	++	++

Numpaisal (2022)	N/A	N/A	++	++	N/A	N/A	+	+	-	++	++
Okamoto (2015)	N/A	N/A	+	+	N/A	N/A	++	++	-	++	-
Park (2015)	N/A	N/A	-	-	N/A	N/A	+	++	++	++	++
Park (2021)	N/A	N/A	N/A	N/A	N/A	N/A	++	-	+	++	++
Poduval (2010)	N/A	N/A	-	-	N/A	N/A	-	-	-	++	-
Pollock (1990)	N/A	N/A	-	-	N/A	N/A	+	-	-	++	-
Pordzik (2020)	N/A	N/A	+	+	N/A	N/A	+	++	+	++	++
Prokopi (2021)	N/A	N/A	-	-	N/A	N/A	++	+	-	++	++
Rafael (2014)	N/A	N/A	-	-	N/A	N/A	-	-	-	++	-
Rajgopal (2014)	N/A	N/A	N/A	N/A	N/A	N/A	++	+	+	++	++
Ramos-Mucci (2020)	N/A	N/A	++	++	N/A	N/A	-	++	-	-	-
Ren (2021)	N/A	N/A	+	+	N/A	N/A	-	++	+	++	++
Richardot (2009)	N/A	N/A	-	-	N/A	N/A	++	++	-	++	++
Rinaldi (1998)	N/A	N/A	-	-	N/A	N/A	-	++	+	++	-
Roller (2015) (ref [72])	N/A	N/A	++	++	N/A	N/A	+	++	+	++	++
Roller (2015) (ref [98])	N/A	N/A	-	-	N/A	N/A	--	++	++	+	-
Saito (2002)	N/A	N/A	N/A	N/A	N/A	N/A	-	++	+	++	++
Santiago (2006)											
Schneider (1994)	N/A	N/A	-	-	N/A	N/A	+	+	-	++	-
Scott (1981)	N/A	N/A	-	-	N/A	N/A	+	-	-	++	-
Scott (1984)	N/A	N/A	-	-	N/A	N/A	++	-	-	++	-
Serrão (2014)	N/A	N/A	++	++	N/A	N/A	++	++	+	++	-
Shi (2020)	+	-	N/A	N/A	+	-	-	+	+	+	++
Sirotti (2023)	N/A	N/A	N/A	N/A	N/A	N/A	++	+	++	++	++
Sladojevic (2016)	N/A	N/A	-	-	N/A	N/A	+	-	+	++	++
Son (2013)	N/A	N/A	N/A	N/A	N/A	N/A	+	-	+	++	++
Sriwatananukulkit (2023)	-	-	N/A	N/A	-	-	++	+	++	++	++
Suga (2022)	N/A	N/A	--	--	N/A	N/A	+	++	+	++	++
Sun (2010)	N/A	N/A	-	-	N/A	N/A	+	-	++	++	++
Sun (2012)	N/A	N/A	-	-	N/A	N/A	++	-	++	++	++
Takahashi (1996)	N/A	N/A	-	-	N/A	N/A	+	++	+	++	++
Takahashi (1998)	N/A	N/A	--	++	N/A	N/A	+	+	+	-	++
Tavallaee (2022)	-	-	-	-	+	-	--	++	++	++	++
Tokumoto (2023)	N/A	N/A	N/A	N/A	N/A	N/A	+	++	-	++	++
Turdean (2017)	N/A	N/A	-	-	N/A	N/A	++	++	+	-	--
Van Linthoudt (1997)	N/A	N/A	N/A	N/A	N/A	N/A	++	++	+	++	++
Voelker (2022)	N/A	N/A	-	-	N/A	N/A	+	++	+	++	++
Walton (1977)	N/A	N/A	-	-	N/A	N/A	-	+	-	-	+
Wang (2018)	N/A	N/A	-	-	N/A	N/A	+	++	+	++	++

Wang (2020)	N/A	N/A	N/A	N/A	N/A	N/A	++	++	++	++	++
Warnecke (2020)	N/A	N/A	-	-	N/A	N/A	-	-	+	++	++
Wei (2021)	+	-	N/A	N/A	-	-	+	++	++	++	++
Worrall (1991)	N/A	N/A	-	-	N/A	N/A	+	++	-	-	-
Worrall (1994)	N/A	N/A	-	-	N/A	N/A	+	++	-	++	++
Zhang (2012)	N/A	N/A	N/A	N/A	N/A	N/A	++	-	+	++	-
Zhang (2019) ref ([174])	+	-	N/A	N/A	++	-	+	+	-	-	++
Zhang (2019) ref ([178])	+	-	N/A	N/A	-	-	-	+	-	-	++
Zhang (2021) ref ([179])	++	-	N/A	N/A	-	-	+	+	+	+	++
Zhang (2021) ref ([175])	+	-	N/A	N/A	-	-	+	+	+	++	++
Zhao (2014)	+	-	N/A	N/A	++	-	+	++	-	++	-
Zhu (2012)	N/A	N/A	--	--	N/A	N/A	-	-	+	++	-

A/EB, attrition/exclusion bias; CB, confounding bias; DB, detection bias; N/A, not applicable; OB, other bias; OHAT, Office of Health Assessment and Translation; PB, performance bias; SB, selection bias; SRB, selective reporting bias.

Table iv. Study characteristics of included human studies.

First author (year)	Country	Joint	Tissue (details)	Stage of disease / OA severity	Control population	No. of participants	Female, %	Mean age, yrs (SD/range)	Mean BMI, kg/m^2	Ref
Abdul Sahib (2017)	Iraq	Knee	Ligament (ACL & PCL)	NR	No	OA: 50	70	NR	NR	[45]
Abraham (2014)	USA	Knee	Meniscus (enthesis)	Advanced	Healthy tissue donors	OA: 7 Control: 8	NR NR	NR 55 (41-61)	NR NR	[61]
Akisue (2002)	Japan	Knee	Ligament (PCL)	Ahlbäck grades 2-5	Cadavers w/o knee OA	OA: 24 Control: 4	38 50	64.2 (40-84) 87 (78-98)	NR NR	[40]
Allain (2001)	France	Knee	Ligament (ACL & PCL)	TKA	No	OA: 45	67	76 (68-84)	NR	[46]
Atik (2016)	Turkey	Knee	Meniscus (medial)	Medial arthroplasty	No	OA: 12	100	64 (59-71)	NR	[83]
Battistelli (2019)	Italy	Knee	Meniscus	KL grade 3-4	Multi-organ donors w/o history of joint disorders	OA: 3 Controls: 3	33 33	Med 72 (IQR 72-73.5) Med 66 (IQR 63-69)	NR NR	[58]
Belluzzi (2020)	Italy	Knee	Fat pad (infrapatellar)	End-stage	ACL reconstruction, med 8 months post-injury	OA: 25 Control: 28	72 25	Med 68 (IQR 62-75) Med 31 (22-42)	Med: 29.5 Med: 23.0	[34]
Cameron (1973)	Canada	Hip	Capsule	End-stage	Not reported	OA: 25 Control: 15	NR NR	NR NR	NR NR	[32]
Campbell (2015)	Canada	Knee	Capsule	Mean KL grade > 3	No	OA: 21	57	Mean >65	NR	[28]
Chang (2005)	Japan	NR	Synovium	Arthroplasty	No	OA: 5	NR	NR	NR	[137]
Cheng (1996)	Belgium	Spine	Intervertebral disc	KL grade 1-4	Cadavers w/o spinal OA	OA: 51 Control: 9	50	67.3 (23-87)	NR	[36]
Christensen (2019)	Denmark	Hip	Synovium	Advanced	No	OA: 6	3	Med 66.5 (IQR 62–69)	Med 30.8	[123]
Cillero-Pastor (2015)	Netherlands	Knee	Synovium	TKA	Adult tissue donors	OA: 3 Control: 3	NR NR	69-82 60-78	NR NR	[114]

Cutolo (1992)	Italy	Knee	Synovium	End-stage	Knee trauma	OA: 4 Control: 4	NR NR	NR NR	NR NR	[115]
Dessombz (2013)	France	Knee	Meniscus (medial)	KL mean grade 4	No	OA: 6	83	74 (SD 9)	28	[62]
DiCesare (1999)	USA	Knee	Synovium	Knee replacement	No	OA: 3	NR	NR	NR	[113]
DiFrancesco (1995)	USA	Hip	Capsule	Advanced	No	OA: 109	57	67.1 (39-92)	NR	[27]
Dijkgraaf (1997)	Netherlands	TMJ	Synovium	Early to advanced	No	OA: 31	81	30.1	NR	[132]
Doerschuk (1999)	USA	Thumb	Ligament (palmar beak)	Mankin grades 3-14	No	OA: 18	72	NR	NR	[51]
Ea (2013)	France	Knee	Synovium	KL grades 0-3	No	Total: 31	NR	NR	NR	[106]
Ene (2015)	Romania	Knee	Synovium	Early and late stage	No	OA: 43	77	49-76	NR	[110]
Exposito Molinero (2016)	Spain	NR	Tendon (Achilles)	NR	No	OA: 24	46	50.7	NR	[147]
Fan (2012)	China	Knee	Synovium	NR	No	OA: 6	50	Med 60 (range 48-77)	NR	[116]
Fink (2007)	Germany	Knee	Skeletal muscle (vastus medialis)	KL grade 4	No	OA: 78	79	68.5 (51-83)	<20: 3 20-24: 12 25-29: 31 >29: 32	[100]
Fischenich (2015)	USA	Knee	Meniscus (medial & lateral)	TKA	No	OA: 24	54	57.8 ± 4.6	31.9	[88]
Folkesson (2020)	Sweden	Knee	Meniscus (posterior horns of medial)	OCS 4 medially; OCS 0-1 laterally	Cadavers (w/o joint disease)	OA: 9 Control: 10	56 50	62.0 (50-75) 51.4 (18-77)	29.0 28.0	[97]
Fuhrmann (2015)	Germany	Knee	Meniscus	TKA	No	OA: 9	67	69.6 (56-80)	NR	[91]
Ghosh (1975)	Australia	Knee	Meniscus	NR	No	OA: 5	NR	NR	NR	[73]

Gouldin (2023)	USA	Knee	Meniscus	Knee replacement	No	OA: 48 (18*)	58 (50*)	69.4 ± 7.5	NR	[87]
Grevenstein (2020)	Germany	Knee	Fat pad (infrapatellar)	TKA	Trauma (ACL rupture)	OA: 14 Control: 11	50 27	63.8 ± 17.6 33.7 ± 14.8	NR	[35]
Haut Donahue (2021)	USA	Knee	Meniscus (medial & lateral enthesis)	TKA	No	OA: 7	NR	40-75	NR	[84]
Heinegård (1968)	Sweden	Knee	Capsule	NR	No	OA: 8	88	60-80	NR	[33]
Hellberg (2023)	Finland, Sweden	Knee	Meniscus (medial, lateral)	Knee replacement	Yes	OA: 10 Control: 10	50 50	NR NR	NR NR	[60]
Herbert (1973)	UK	Hip	Capsule	NR	Cadavers w/o joint disease	OA: 12 Control: 11*	NR NR	30-70 NR	NR NR	[31]
Hino (1995)	Japan	NR	Synovium	NR	No	OA: 4	NR	NR	NR	[138]
Hino (2020)	Japan	Knee	Meniscus (posterior root)	NR	No	OA: 7	57	75 (67-86)	NR	[78]
Ibrahim (2019)	Sweden	Shoulder	Tendon (biceps & subscapularis	Total shoulder arthroplasty	Proximal humeral fracture	OA: 13 Control: 13	NR NR	Med 67 Med 70	NR NR	[146]
Ibrahim (2021)	Sweden	Hip	Tendon (Gluteus Medius)	Total hip arthroplasty	Femoral head fracture	OA: 29 Control: 25	66 76	70 73	NR NR	[149]
Ishizuka (2016)	Japan	Knee	Meniscus	TKA	No	OA: 30	57	71	NR	[79]
Itokazu (1998)	Japan	NR	Synovium	NR	Traumatic injury	OA: 22 Control: 16	41 25	59 21	NR NR	[140]
Jacquet (2018)	France	Knee	Meniscus	TKA	No	OA: 5	40	64	23.2	[81]
Jacquet (2019)	France	Knee	Meniscus (lateral)	Advanced medially, KL grade < 2 laterally	No	OA: 24	50	64	NR	[96]
Johnson (2001)	USA	Knee	Meniscus (medial)	Advanced (joint replacement)	Cadavers	OA: 5 Control: 5	NR NR	NR NR	NR NR	[63]

Karjalainen (2021)	Finland	Knee	Meniscus (medial & lateral)	Outerbridge IV medially; 0/I medially	Cadavers	OA: 10 Control: 10	50 50	63 ± 7 51 ± 17	NR	[82]
Karube (1981)	Japan	Knee	Meniscus	NR	NR	OA: 3 Control: 17[#]	NR	48-62 13-62[#]	NR NR	[93]
Katsuragawa (2010)	Japan	Knee	Meniscus (ant. horn and body of medial and lateral)	End-stage	Cadavers w/o joint disease	OA: 40 Control: 22	NR NR	NR 84 (73-92)	NR NR	[80]
Kaufmann (2003)	Germany	Knee	Synovium	Knee replacement	No	OA: 21	76	71 (49-82)	NR	[111]
Kiraly (2017)	USA	Knee	Meniscus (posterior medial)	TKA	No	OA: 10	NR	NR	NR	[64]
Klareskog (1986)	Sweden	NR	Synovium	Arthroplasty	No	OA: 15	NR	NR	NR	[135]
Kodama (2018)	Japan	Knee	Meniscus (ant. & post. sections)	KL grade 4 (TKA)	No	OA: 26 menisci	84	76 ± 6.7 (68-84)	NR	[55]
Komro (2020)	USA	Knee	Ligament (ACL)	OCS mean 3.6 (range 3.2-4.0)	Cadaver (normal macroscopic ACL)	OA: 6 Control: 16	100 50	66 ± 9.6 75 ± 12.3	37.6 23.0	[38]
Konttinen (1999)	Finland	Hip	Synovium	NR	ACL tear (2), meniscal injury (3)	OA: 10 Control: 5	70 60	71 (41-84) 41 (22-53)	NR NR	[125]
Konttinen (2001)	Finland	Hip	Synovium	THA	No	OA: 10	60	70 (40-83)	NR	[122]
Kragstrup (2019)	USA	Knee	Synovium	KL grade 2-4	No	OA: 12	NR	NR	NR	[117]
Krawetz (2022)	Canada	Knee	Synovium	KL grade 3-4	Cadavers (w/o cartilage damage)	OA: 8 Control: 8	50 38	51-82 32-80	NR NR	[104]
Kriegsman (2004)	Germany	NR	Synovium	NR	No	OA: 3	NR	NR	NR	[139]
Kumagai (2012)	USA	Knee	Ligament (ACL & PCL)	Koshimoto's grade 3-5	No	OA: 28	82	77 (67-84)	NR	[37]

Kwok (2014)	USA	Knee	Meniscus	OARSI score 4	Healthy donors (OARSI 0-1)	OA: 3 Control: 3	NR NR	75 (61-90) 31 (20-41)	NR NR	[89]
Levy (2013)	USA	Knee	Ligament (ACL & PCL)	OCS score 0-4	Cadavers w/o joint degeneration	65 (111 OA & 9 control knees)	54	67 ± 19 (23-92)	24.8	[42]
Li (2000)	Finland	Hip	Synovium	Hip replacement	No	OA: 10	NR	NR	NR	[124]
Limberg (2022)	USA	Knee	Capsule (posterior)	Total knee replacement	No	OA: 14	36	65 ± 9	34 ± 5	[29]
Lopez-Franco (2016)	Spain	Knee	Meniscus (medial)	Knee replacement	No	OA: 31	74	72 ± 6.7 (60-84)	NR	[65]
Mapp (1985)	UK	Knee & hip	Synovium	NR	No	OA: 4	100	60.8 (46-69)	NR	[128]
Marczak (2017)	Poland	Knee	Ligament (PCL)	Ahlbäck grade 3-5	Cadavers w/o joint damage	OA: 50 Control: 10	80 70	71 (53-84) 72 (67-78)	NR NR	[43]
Martins (2018)	Brazil	Knee	Ligament (PCL)	Ahlbäck grade 1-5	No	OA: 85	81	70 (53-87)	NR	[47]
Masuda (1991)	Japan	Knee	Synovium, meniscus	NR	No	OA: 10	NR	76	NR	[94]
Mattiello-Sverzut (2013)	Brazil	Knee	Skeletal muscle (vastus lateralis)	KL grade 2.3 ± 1.2	No	OA: 6	33	62 ± 5	28.1	[103]
Mazzocca (2013)	USA	Shoulder	Tendon (long head of biceps)	NR	Cadavers w/o joint damage	OA: 9 Control: 9	22 56	59 ± 11.6 58 ± 14.7	NR NR	[148]
McDaniel (2017)	USA	Knee	Meniscus (medial & lateral)	Knee replacement	Cadavers w/o joint damage	OA: 14 Control: 14	50 64	62 ± 7.7 67 ± 10.6	34.6 NR	[59]
Meknas (2012)	Norway	Hip Tendon	Tendon (internal obturator)	NR	Femoral fracture	OA: 10 Control: 10	60 80	Med 60 (48-75) Med 83 (60-90)	NR NR	[145]
Melrose (2008)	Australia	Knee	Meniscus (medial & lateral)	Joint replacement	Cadavers w/o cartilage damage	OA: 17 Control: 6	11 NR	77.8 ± 5.4 (70-88) (60-75)	NR NR	[57]

Mine (2013)	Japan	Knee	Meniscus	TKA	No	OA: 12	NR	NR	NR	[76]
Mobargha (2014)	Sweden	Thumb	Ligament (volar anterior oblique & dorsoradial)	Eaton stage 2-3	No	OA: 11	91	67 (51-83)	NR	[52]
Monibi (2021)	USA	Knee	Meniscus (posterior medial)	Knee replacement	No	OA: 8	63	65 ± 5.5	NR	[92]
Musumeci (2014)	Italy	Knee	Meniscus (medial & lateral)	KL grade 2-3	ACL reconstruction	OA: 40 Control: 9	38 44	Med 68 (51-76) Med 60 (45-66)	NR NR	[95]
Nagata (2000)	Japan	Knee	Meniscus (medial)	KCS score: mean 52.6	No	OA: 11	73	79 (73-86)	NR	[85]
Nakahara (2013)	USA	Knee	Ligament (ACL)	KCS score 2-4	Normal cadaver, aged controls (cartilage score 1)	OA: 16 Cadaver: 13 Aged: 8	50 Unclear 63	80 ± 11.4 37 ± 11.0 77 ± 12.9	NR NR NR	[44]
Nakamura (2022)	Japan	Knee	Ligament (ACL)	KL grade 3-4	No	OA: 65 (82 ACLs)	83	71.7 (56-85)	26.0 (16.3-38.4)	[39]
Nakashima (1998)	Japan	Knee	Synovium	KCS score (2-4)	No	OA: 9	67	57 ± 8 (47-70)	NR	[107]
Nelissen (2001)	Netherlands	Knee	Ligament (PCL)	Ahlbäck grade 3-5	No	OA: 11	82	75 (60-85)	NR	[48]
Nikkari (1995)	Finland	Knee	Synovium	Knee replacement	No	OA: 6	NR	63	NR	[118]
Nishida (1995)	Japan	Knee	Synovium	Knee replacement	No	OA: 18	83	72 (62-86)	NR	[119]
Noehren (2018)	USA	Knee	Skeletal muscle (vastus lateralis)	KL grade 2-3	KL grade 0-1	OA: 24 Control: 15	42 67	60 ± 5.5 (52-73) 64 ± 6.9 (54-74)	28.4 26.9	[101]
Numpaisal (2022)	Thailand, Taiwan	Knee	Meniscus (non-degraded)	TKA	No	OA: 10	100	68.7	NR	[56]

Okamoto (2015)	Japan	TMJ	Synovium	NR	Cancer patient cadavers	OA: 5 Control: 3	60 67	60 (20-72) 64 (61-70)	NR NR	[133]
Park (2015)	South Korea	Knee	Meniscus (medial posterior root)	KL grade 3-4	Normal joint cadavers	OA: 99 Control: 3	NR 33	(50-85) 54 (47-61)	NR NR	[66]
Park (2021)	South Korea	Knee	Meniscus (medial & lateral)	Knee replacement	No	OA: 12	100	73 (65-82)	NR	[99]
Poduval (2010)	Finland	NR	Synovium	NR	Knee trauma	OA: 5 Control: 5	NR NR	NR NR	NR NR	[142]
Pollock (1990)	UK	Knee & hip	Synovium	NR	Trauma	OA: 7 Control: 4	71 50	69 (58-83) 38 (27-60)	NR NR	[127]
Pordzik (2020)	Germany	Knee	Meniscus (medial & lateral)	KL grade 4	NR	OA: 26 Control: 14	73 NR	Overall: 72 ± 6.7	NR	[90]
Prokopi (2021)	Greece, USA	Knee	Meniscus (medial or lateral)	Meniscectomy or knee replacement	No	OA: 21	52	53 (24-84)	NR	[70]
Rafael (2014)	Portugal	Knee	Synovium	Knee replacement	Normal joint cadaver	OA: NR Control: NR	NR NR	NR NR	NR NR	[105]
Rajgopal (2014)	India	Knee	Ligament (PCL)	KCS mean 42	No	OA: 62	74	67 ± 11 (49-91)	NR	[49]
Ren (2021)	China	NR	Synovium	NR	No	OA: 12	75	67.9 ± 1.98	NR	[143]
Richardot (2009)	France	Knee	Synovium	Ahlbäck grade 3-5	No	OA: 4	100	(54-73)	NR	[109]
Rinaldi (1998)	Germany	Knee & hip	Synovium	NR	No	OA: 18	NR	NR	NR	[131]
Roller (2015)	USA	Knee	Meniscus (medial & lateral)	KL grade mean 3.94	Cadaver or amputation (KL 0)	OA: 23 Control: 5	NR NR	60 (36-81) 77 (64-87)	NR NR	[72]
Roller (2015)	USA	Knee	Meniscus	Mild to severe OA	Normal joint cadaver	OA: 6 Control: 3	50 NR	(44-69) (64-78)	NR NR	[98]
Saito (2002)	Japan	Knee	Synovium (medial & lateral)	Advanced disease	No	OA: 21	NR	64 (47-78)	NR	[108]
Santiago (2006)	Spain & France	NR	Synovium	NR	No	OA: 8	NR	NR	NR	[141]

Schneider (1994)	Germany	NR	Synovium	NR	Meniscal lesions	OA: 8 Control: 31	NR NR	NR NR	NR NR	[134]
Scott (1984)	UK	NR	Synovium	NR	Meniscal lesions	OA: 10	60	(37-72)	NR	[136]
Scott (1981)	UK	Hip & knee	Synovium	NR	No	OA: 8	63	61 (37-72)	NR	[129]
Serrao (2014)	Brazil	Knee	Skeletal muscle (vastus lateralis)	KL grade 1-2	Healthy controls	OA: 18 Control: 17	NR NR	51 ± 6.3 52 ± 8.1	29.5 27.3	[102]
Sirotti (2023)	Italy, Switzerland, Denmark, Spain, Mexico, USA, France, UK, New Zealand, Australia	Knee	Meniscus (medial and lateral)	Knee replacement	No	OA: 51	63	74 ± 8	NR	[71]
Sladojevic (2016)	Bosnia & Herzegovina	Knee	Meniscus (medial & lateral)	Advanced disease	No	OA: 35	86	69.3 (56-78)	30.8	[77]
Son (2013)	USA	Knee	Meniscus (medial & lateral)	TKA	No	OA: 14	57	65	NR	[74]
Suga (2022)	Japan	Spine	Ligament (transverse)	Moderate-severe (Betch et al)	No	OA: 28	61	75.1 ± 9.5	NR	[53]
Sun (2010)	USA	Knee	Meniscus (posterior medial)	End-stage disease	No	OA: 8	6	57 (42-70)	NR	[67]
Sun (2012)	USA	Knee	Meniscus (medial)	End-stage disease	No	OA: 8	6	57 (42-70)	NR	[54]
Takahashi (1996)	Japan	Knee	Synovium	TKA	No	OA: 10	NR	58-79	NR	[112]
Takahashi (1998)	Japan	Knee	Meniscus (central & peripheral)	TKA	No	OA: 21	NR	69 (40-84)	NR	[68]

Tokumoto (2023)	Japan	Knee	Ligament (PCL)	KL grade 3-4	No	OA: 30	63	73.5 (66-89)	NR	[50]
Turdean (2017)	Romania	Hip	Synovium	KL grade 3-4	No	OA: 57	44	64 (24-83)	NR	[121]
Van Linthoudt (1997)	USA	Hip & knee	Synovium	KL grade 2-4, mean 3.25	No	OA: 16	0	68 (54-76)	NR	[126]
Voelker (2022)	Germany	Spine	Capsule (facet joint), ligament (ligamentum flavum)	Fujiware classification 3-4, Pfirrman classification 3-5	Cadaver	OA: 10 Control: 5	60 40	61 ± 14.9 87 ± 8.6	NR	[30]
Wang (2020)	UK	Knee	Meniscus (medial)	TKA	No	OA: 10	40	66 (46-87)	NR	[86]
Wang (2018)	China	Knee	Synovium	TKA	Lower limb amputation	OA: 31 Control: 5	Overall: 20	Overall: (48-69)	NR	[120]
Warnecke (2020)	Germany	Knee	Meniscus (lateral)	TKA	No	OA: 24	67	67 ± 9.0	29	[75]
Worrall (1991)	UK	NR	Synovium	TKA	Malignancy	OA: 4 Control: 5	63 NR	62 NR	NR NR	[144]
Worrall (1994)	UK	Knee & hip	Synovium	Replacement arthroplasty	(Ankle, knee, elbow)	OA: 6 Control: 6	NR NR	NR NR	NR NR	[130]
Zhang (2012)	USA	Knee	Meniscus	NR	No	OA: 18	NR	(50-81)	NR	[69]
Zhu (2017)	China	Knee	Ligament (ACL)	TKA	No	OA: 20	NR	65 ± 5.6	NR	[41]

*Note on the control group of Herbert (1973): although 15 participants were in the control group in total, results in this review are based on the included adults only (11 participants).

#Note on the control group of Karube (1981): although non-adult participants were included in the study, the results in this review are based exclusively on the age groups with adults only.

ACL, anterior cruciate ligament; KCS, Knee Society Clinical Grading System; KL grade, Kellgren-Lawrence grade; Med, median; NR, not reported; OA, osteoarthritis; OARSI, Osteoarthritis Research Society International; OCS, Outerbridge Classification System; PCL, posterior cruciate ligament; TKA, total knee arthroplasty; TMJ, temporomandibular joint.

Table v. Study characteristics of included animal studies. Joint of interest is the knee joint, unless otherwise specified. Age/time is reported in days (d), weeks (w), months (m), or years (y).

Study (year)	Country	Species (strain)	OA model	Tissue (details)	Stage of disease / OA severity	Control population	No. of animals	Female, %	Age at start of study (w/m/y)	Follow-up	Ref
Almasry (2015)	Saudi Arabia	Rat (Wistar albino)	Meniscectomy	Synovium	Early stage	Non-operated	OA: 15 Control: 15	0 0	Adult	6w	[181]
Anderson-Mackenzie (1999)	UK	Mouse (CBA, STR/ort)	STR/ort	Ligament (ACL & PCL)	NR	CBA mice	OA: 16 Control: NR	0 0	22/30/40/50 w 22/30/40/50 w	0w	[153]
Bansal (2020)	USA	Pig (Yucutan minipig)	DMM	Meniscus	NR	Sham surgery	OA: 13 Control: 11	0 0	6.8m 6.8m	1 & 3m	[168]
Bansal (2021)	USA	Pig (Yucutan minipig)	DMM	Meniscus	NR	Sham surgery	OA: 5-7 per time period Control: 5-6 per time period	0 0	7.4±1.2m 7.4±1.2m	1#, 3#, 6m	[169]
Barton (2021)	Canada	Sheep (Suffolk cross)	Partial ACL transection	Ligament (PCL), synovium	NR	Non-operated	OA: 11 Control: 6	100 100	3-5y 3-5y	20 & 40 w	[157]
Bedingfield (2021)	USA	Mouse (C57BL/6)	Mechanical loading	Meniscus, synovium	DJD score 5	Non-loaded	NR NR	NR NR	6m 6m	NR NR	[158]
Bryk (2021)	Poland	Rat (Wistar)	MIA	Synovium	NR	Non-injected	OA: 5-8 per	0 0	NR NR	2-28d	[183]

							time period Control: 1-2 per group				
Castrogiovanni (2019)	Italy	Rat (Wistar)	ACLT	Synovium	OARSI score 3.25 ± 0.71	NR	OA: 8 Control: 8	0 0	Adult Adult	14w	[184]
Catheline (2021)	USA	Mouse (C57BL/6J)	Aged	Meniscus (medial, lateral, anterior, posterior)	Modified OARSI score: ~0.7 (male) and ~0.5 (female)	Young	OA: 5 per group per gender Control: 5 per group per gender	0/100 0/100	24-27m 3, 6, 15m	n/a	[160]
Cui (2023)	Australia, Finland, Switzerland, Canada	Rabbit (NZW)	ACLT	Ligament (MCL & LCL)	NR	Non-operated	OA: 11 Control: 16	100 100	12m 12m	8w	[154]
Dai (2020)	China	Rat (Sprague-Dawley)	ACLT	Synovium (ant. & post.)	Early to late-stage OA	Sham surgery	OA: 36 Control: 36	0 0	12w 12w	4, 8 & 12w	[182]
Endo (2018)	Japan	Rat (Wistar)	ACLT	Meniscus (medial & lateral)	OARSI score 1	Sham surgery	OA: 12 Control: 12	0 0	10w 10w	3w	[167]
Funakoshi (2007)	Canada	Sheep (Suffolk cross)	ACL + MCL transection	Ligament (ACL & PCL)	NR	Non-operated	OA: 5 Control: 4	100 100	3y 3y	20w	[156]
Gamal (2019)	Egypt	Rat (albino)	Cartilage defect	Synovium	NR	Non-operated	OA: 10	0 0	4-5m 4-5m	4 & 6w	[173]

							Control: 10				
Hellio Le Graverand (2001)	France	Rabbit (NZW)	ACLT	Meniscus (medial & lateral)	NR	Non-operated	OA: 24 Control: 12	100 100	12m 12m	3 & 8w	[163]
Hellio Le Graverand (2001)	Canada	Rabbit (NZW)	ACLT	Meniscus (medial)	NR	Non-operated	OA: 16 Control: 16	100 100	12m 12m	1, 2, 3, 4w	[162]
Krawetz (2022)	Canada	Rat (NR)	DMM	Synovium	NR	Sham	OA: 5 Control: 5	40 40	12w 12w	4w	[104]
Lapadula (1995)	Italy	Rabbit (Flanders giant)	Vitamin A injection	Synovium	Early stage	Untreated	OA: 12 Control: 4	0 0	8m 8m	3, 6, 9d	[186]
Lee (2020)	USA	Mouse (BALB/cByJ)	DMM	Meniscus	NR	Sham surgery	OA: unclear * Ctrl: unclear *	* *	12w 12w	5w	[157]
Lee (2021)	Korea	Rat (Sprague-Dawley)	MIA	Muscle (rectus femoris)	NR	Untreated	OA: 7 Control: 8	0 0	6-7w 6-7w	56d, 87d	[171]
Levillain (2017)	France	Rabbit (NZW)	ACLT	Meniscus (medial)	Early stage	Non-operated	OA: 6 Control: 6	0 0	6m 6m	8w	[165]
Levillain (2017)	France	Rabbit (NZW)	ACLT	Meniscus (medial)	Early stage	Non-operated	OA: 6 Control: 6	0 0	6m 6m	8w	[166]
Li (2020)	China	Rat (Sprague-Dawley)	MIA	Synovium	NR	Sham surgery	OA: 6 Control: 6	0 0	8w 8w	8w	[180]
Li (2021)	China	Rat (Sprague-Dawley)	MIA	Synovium	NR	Sham (saline)	OA: 10 Control: 10	0 0	NR NR	28d	[176]

Loeser (2013)	USA	Mouse (C57BL/6)	DMM	Meniscus, ligament, capsule, synovium	Early to end-stage	Sham surgery	OA: 36 Control: 36	0 0	12w 12w	2, 4, 8, 16w	[150]
McErlain (2008)	Canada	Rat (Sprague-Dawley)	ACLT	Tendon (patellar)	NR	Sham surgery	OA: 15 Control: 3	0 0	3w 3w	1, 2, 3, 4, 5m	[187]
Miller (2014)	Canada	Rabbit (NZW)	ACLT	Ligament (MCL)	NR	Non-operated	OA: 6 Control: 6	100 100	1y 1y	6w	[155]
Muschter (2020)	Germany	Mouse (C57BL/6)	DMM	Meniscus	NR	Sham surgery	OA: 72 Control: 72	0 0	8-10w 8-10w	2, 4, 8, 12w	[159]
Ramos-Mucci (2020)	UK	Mouse (CBA, STR/ort)	STR/ort	Meniscus, ligaments (ACL, MCL, LCL)	OARSI grade 1-6	CBA mice	OA: 29 Control: 12	0 0	27, 37, 40w 26, 40w	N/A	[151]
Shi (2020)	China	Rabbit (NZW)	Adapted Videman method	Skeletal muscle (rec. fem & biceps fem)	NR	Non-operated	OA: 6 Control: 6	0 0	NR NR	10w	[170]
Sriwatananukulkit (2023)	Thailand	Rat (Sprague-Dawley)	MIA	Synovium / infrapatellar fat pad	NR	Sham (saline)	OA: 12 Control: 12	0 0	7w 7w	2, 4, 8w	[177]
Tavallaee (2022)	Canada, USA, Slovakia	Mouse (C57BL/6J)	DMM	Synovium	NR	Sham surgery	OA: 10 Control: 9	OA: 0 Control: 0	10-12w 10-12w	5w	[172]
Walton (1977)	UK	Mouse (CBA, STR/ort)	STR/ort	Ligament	NR	CBA mice	OA: 351 Control: 348	36 28	4+m 4+m	NR NR	[152]

Wei (2021)	China	Rabbit (domestic)	Modified Hulth method	Synovium	OARSI score ~5 (4w) to ~11 (12w)	Sham surgery	OA: 15 Control: 5	NR NR	6m 6m	4, 12w	[185]
Zhang (2021)	China	Rat (Sprague-Dawley)	ACLT, DMM, MIA	Synovium	NR	'Normal'	Total: 80	0	NR	2, 4w	[179]
Zhang (2021)	China	Rat (Sprague-Dawley)	MIA	Synovium	NR	'Normal'	OA: 8 Control: 8	0 0	2m 2m	5w	[175]
Zhang (2019)	China	Rat (Sprague-Dawley)	MIA	Synovium	NR	Saline injection	OA: 6 Control: 6	100 100	3m 3m	4w	[174]
Zhang (2019)	China	Rat (Sprague-Dawley)	ACLT	Synovium	NR	'Normal'	OA: 8 Control: 8	0 0	3m 3m	4w	[178]
Zhao (2014)	China	Rabbit (Chinese)	Cartilage injury	Meniscus (interior)	NR	Sham surgery	OA: 12 Control: 12	100 100	20m 20m	1-6w	[164]

*Lee et al (2020): 11 animals (5 male and 4 female) were used across three groups: 2 OA groups and 1 control group.

#Bansal et al (2021): animals in one- and three-month follow-up groups were already reported on in Bansal et al (2020).

ACL, anterior cruciate ligament; ACLT, anterior cruciate ligament transection; DJD, degenerative joint disease; DMM, destabilization of the medial meniscus; LCL, lateral cruciate ligament; MCL, medial cruciate ligament; MIA, monoiodoacetate; NR, not reported; NZW, New Zealand White; OARSI, Osteoarthritis Research Society International; PCL, posterior cruciate ligament.