

REVIEW – KNEE OA PAIN

Table 2. Alphabetical (non-comprehensive) compilation of biomarkers and interventions investigated in the context of knee osteoarthritis

BIOMARKERS			
BIOMARKERS ELEVATED IN OA	LOE* positive †		LOE negative ‡
Cartilage degradation-regeneration			
ADAMTS5	5 ¹	6 ²	4 ³ , 9 ⁴
ARGS	4 ⁵		5 ⁶
Bradykinin			4 ³
Cathepsins	7 ⁷		
CCL2	6 ⁸		
CD163			4 ⁹
CGRP	5 ¹⁰		4 ³
Chemokines	5 ¹¹		
C2M	5 ⁶		3 ¹²
Coll2-1	3 ¹³ , 5 ¹⁴		
Coll2-NO2	5 ¹⁴		
Collagenase-3	6 ¹⁵		
COMP	3 ¹⁶ , 4 ¹⁷		1 ¹⁸
CX3CL1 / fractalkine	2 ¹⁹		
ECM breakdown products	7 ²⁰		
EZH2	7 ²¹		
HA	4 ¹⁷		
Hsp70	3 ²²		
HtrA1	7 ²³		
Indian Hedgehog	5 ²⁴		
Keratan sulfate	4 ¹⁷		
M-CSF			4 ³
MMP-1			1 ¹⁸
MMP-3	3 ¹⁶	4 ²⁵	1 ¹⁸ 4 ³

MMP-13		4 ³
NF- κ B	5 ²⁴	
NO	5 ²⁶	7 ²⁷
Osteocalcin / N-MID	7 ²⁸	
Osteopontin		7 ²⁹
PIIANP	4 ³⁰	
PIIBNP	4 ³¹	
PGE ₂	6/7 ³²	
PRO-C1		3 ¹²
PRO-C2	3 ³³ , 4 ³¹ , 7 ³¹	3 ¹²
Proteoglycan	2 ³⁴ , 7 ³⁵	
ROS	5 ³⁶	
Runx2	5 ²⁴	
TG-2	6 ³⁷ , 7 ^{38, 39}	
TLR/RAGE Ligands	7 ³⁵	
Type II collagen	7 ⁴⁰	
Type X collagen	7 ⁴⁰	7 ²⁹
uCTX-II	4 ³⁰	
YKL-40	3 ¹⁶	
Other relevant tissues/cells/molecules		
Bone remodeling and inflammation		
C10C	3 ¹²	
sCTX-I	3 ⁴¹	
uALPHA-CTX	4 ⁴²	
uCTX-II	4 ⁴³	
uNTX-I	4 ⁴³	
Connective tissue sclerosis and thickening		
C1M	4 ⁴⁴	
C3M		4 ⁴⁵
Macrophages / Mast cells		
Dorsal root ganglia	6 ⁴⁶	
Synovium	5 ^{47, 48} , 6 ⁴⁹	
Synovitis	3 ⁵⁰ , 4 ^{51, 52} , 5 ⁵³⁻⁵⁶	
Tryptase	3 ⁵⁷	

Mast cells	6 ⁴⁹	
Macrophages (various joint tissues)	5 ^{47, 48}	
TREM-1		6 ⁵⁸
TREM-2	5 ⁵⁶ , 6 ⁵⁸ , 7 ⁵⁹	
Proinflammatory Cytokines		
IL-1 β	4 ³	
IL-6	3 ⁶⁰ , 4 ^{3, 44}	
IL-15	3 ⁶¹	
IL-17	4 ⁶²	
IL-18		3 ¹⁶
IL-20	3 ¹⁶	
TNF α	4 ³	
Inflammatory serum markers		
hsCRP	4 ⁶²	
CRPM		4 ^{9, 45}
Inflammatory markers including CRP	4 ⁶³ , 5 ⁶⁴	
LAR	4 ⁶⁵	
Low grade inflammation	5 ⁶⁶	
usCRP	4	
Growth Factors		
FGF (see also "Sprifermin")	5 ⁶⁷ , 7 ⁶⁸	
IGF-1	5 ⁶⁹	
VEGF	5 ²⁴ , 7 ⁷⁰	
Neuronal markers		
BDGF	4 ⁷¹	
BDNF	3 ⁷² , 6 ⁷³	
NGF	3 ⁷⁴	
Neuropeptide Y		4 ³
Substance P		4 ³
Biomechanical markers		
Actimetry		5 ⁷⁵
Gait analysis	3 ^{76, 77 78}	5 ⁷⁹
INTERVENTIONS		

ORAL PREPARATIONS	LOE* positive †	LOE negative ‡
Acetaminophen	1A ⁸⁰	1A ⁸¹
Alpha-adrenergic blockers	4 ⁸²	
Antibiotics		
Doxycycline	1 ⁸³	5 ⁸⁴ 1 ⁸⁵
Anticoagulants	4 ⁸²	
Antihistamines (H ₁)	4 ⁸²	3 ⁸⁶
Antilipemics (excluding statins and fibric acid)	4 ⁸²	
Antineoplastic agents	4 ⁸²	
Calcitonin (salmon)		1 ⁸⁷
Cannabinoids		6 ⁸⁸
Collagen hydrolyzates and ultrahydrolyzates	5 ⁸⁹	
Devil's claw	4 ⁹⁰	
Gabapentinoids		
Gabapentin	1 ⁸¹	
Pregabalin	1 ⁹¹	1 ⁹²
Glucosamine	1A ⁹³	
Glycosaminoglycans		
Chondroitin sulfate	5 ^{94, 95}	
Green-lipped mussel	6 ⁹⁶	
HA + Glucosamine + Chondroitin	1 ⁹⁷	
HA + Platelet-rich plasma	1A ⁹⁸	
Interleukin inhibition		
IL-1β		
Canakinumab	3 ⁹⁹ , 5 ¹⁰⁰	
Diacerein	1A ⁹³ , 1 ^{101, 102}	
Lutikizumab		1A ¹⁰³ , 1 ¹⁰⁴ , 5 ¹⁰⁰
NSAIDs	5 ¹⁰⁵	
Non-selective Cyclooxygenase 2 Inhibitors		
Naproxen	1A ⁸⁰	
Selective Cyclooxygenase 2 Inhibitors	5 ¹⁰⁶	
Aceclofenac	1 ⁹¹	
Meloxicam		1 ⁹²

Opioids		1A¹⁰⁷, 8¹⁰⁸
Tramadol	1A¹⁰⁹	1A¹¹⁰
SNRI	1A¹¹¹	
Duloxetine	1A^{81, 103}	1A¹¹²
SSRI	4⁸²	
Sympatholytics	5¹¹³	
TCA		1A¹¹¹
Nortriptyline		1¹¹⁴
TNF α monoclonal antibodies		
Adalimumab		5¹¹⁵
Infliximab		5¹¹⁵
Etanercept		5¹¹⁵
Turmeric extract	5¹¹⁶	
Vitamins		
Vitamin D	1¹¹⁷	5¹¹⁸
INTRA-ARTICULAR PREPARATIONS		
Botulinum toxin type A	1A¹¹⁹	
Bradykinin-receptor antagonists		
Icatibant	5¹⁰, 7¹²⁰	
MEN16132	7¹²⁰	
Capsaicin / CNTX-4975	1¹²¹, 5¹²²	
Corticosteroids	1A⁸⁰	
Human fibroblast growth factor 18		
Sprifermin	1¹²³, 3¹²⁴, 7¹²⁵	
Hyaluronic acid (derivatives = viscosupplementation)	1A⁸⁰	1A¹²⁶
LNA043	1¹²⁷	
Melatonin	5²⁶, 6¹²⁸	
Mesenchymal stem cells	5¹²⁹	1A¹³⁰
Nanofat	6¹³¹	
NMDA receptor antagonists		
Ketamine	6¹³²	
Platelet-rich plasma	1A⁸⁰	
ROR2 siRNA	6¹³³	
TrkB-Fc chimera	7⁷³	

Wnt pathway modulator		
Lorecivivint	1 ¹³⁴	
INTRA-PERITONEAL PREPARATIONS		
Capsazepine (gender-specific)	6 ¹³⁵	
SUBCUTANEOUS PREPARATIONS		
Anti-immunoglobulin E		
Omalizumab	4 ¹³⁶	
Anti-nerve growth factor antibody		
Fulranumab	1 ¹³⁷	
Fasinumab	1 ¹³⁸	
Tanezumab	1 ¹³⁹ , 5 ^{140, 141}	
iPTH	6 ^{142, 143}	
TOPICAL AGENTS		
Capsaicin	1 ¹⁴⁴ , 5 ¹⁴⁵	
NSAIDs	1A ¹⁴⁶	
Diclofenac	5 ^{147, 148}	
Trolamine salicylate	1 ¹⁴⁹	1 ¹⁵⁰
Paraffin wax	1 ¹⁵¹	
IN VITRO MODELS		
rPDGF-BB	6 ¹⁵²	
NON-INVASIVE INTERVENTIONS		
Acupuncture	5 ^{153, 154}	
Neuromodulation techniques		
Peripheral nerve (field) stimulation	5 ¹⁵⁵	
TENS	1 ¹⁵⁶ , 5 ¹⁵⁷	
TMS	4 ¹⁵⁸	
Photobiomodulation therapy		5 ¹⁵⁹
Radiofrequency ablation	1A ^{160, 161}	
Spa therapy	5 ¹⁶²	
Thermotherapy		
Bath therapy	1A ¹⁶³	
Cold pack	1 ¹⁶²	5 ¹⁶⁴
Contrast therapy	1 ¹⁶²	
Hot pack / heat	1 ¹⁶²	5 ¹⁶⁴

INVASIVE INTERVENTIONS		
Genicular artery embolization	5 ¹⁶⁵	
TKA ^{166, 167}	#	
PSYCHOLOGICAL / PSYCHIATRIC INTERVENTIONS		
Cognitive behavioral therapy	1A ¹⁶⁸ , 5 ¹⁶⁹	
ACTIVITY		
Balance training	1 ^{170, 171}	
Cane	2 ¹⁷² , 3 ¹⁷³	
Exercise	1A ^{168, 174} , 1 ^{18, 175-177} , 5 ¹⁷⁸	
Self-efficacy / self-management programs	3 ¹⁷⁹ , 5 ¹⁸⁰	
Kinesio taping	1A ¹⁸¹ , 1 ¹⁸	
Tai Chi	1 ¹⁸² , 5 ¹⁸³	
Tibiofemoral knee brace	3 ¹⁸⁴	2 ¹⁸⁵
Weight loss	1 ¹⁸⁶ , 5 ¹⁸⁷	

TKA generally considered beneficial, due to the variability in focus of studies (e.g., TKA in general, TKA combined with nonsurgical treatment, TKA combined with psychological support) and the large body of literature details for TKA are not incorporated in this table.

*AHRQ: 1A = Meta-analysis or multiple well-designed controlled studies, 1 well-designed randomized controlled studies, 2 = well-designed non-randomized controlled trial (quasi-experiments), 3 = observational studies with controls (retrospective studies, interrupted time-series studies, case-control studies, cohort studies with controls), 4 = observational studies without controls (cohort studies without controls and case series); additionally 5 = narrative/systematic review, 6 = animal model, 7 = in vitro studies, 8 = editorial.

† Defined as successful biomarker/intervention in the referenced studies

‡ No evidence for biomarker/intervention

BIOMARKERS/INTERVENTIONS ASSOCIATED WITH OA PAIN / BIOMARKERS/INTERVENTIONS NOT ASSOCIATED WITH KNEE OA PAIN / BIOMARKERS/INTERVENTIONS WITH CONFLICTING RESULTS CONCERNING KNEE OA PAIN

BIOMARKERS/INTERVENTIONS ASSOCIATED WITH STRUCTURAL OA / BIOMARKERS/INTERVENTIONS NOT ASSOCIATED WITH STRUCTURAL OA / BIOMARKERS/INTERVENTIONS WITH CONFLICTING RESULTS CONCERNING STRUCTURAL OA

Abbreviations: ADAMTS5, a disintegrin and metalloproteinase with thrombospondin motifs 5; AHRQ, The Agency for Healthcare Research and Quality (see below); ANGPTL3, angiopoietin-like protein 3; ARGS, Alanine-Arginine-Glycine-Serine (ARGS) aggrecan; BDNF, brain-derived neurotrophic factor; C2M, a fragment of type II collagen released by MMP; C10C, collagen biomarker measuring type X collagen; CBT, cognitive behavioural therapy; CCL2, C-C Motif Chemokine Ligand 2; CGRP, calcitonin gene related peptide; Coll2-1/Coll2-1 NO2, type II collagen-specific biomarkers of type II collagen degradation (Coll2-1) and joint inflammation (Coll2-1 NO2); COMP, serum cartilage oligomeric matrix protein; CRP, C-reactive protein; CRPM, neo-epitope of MMP-mediated degradation c-reactive protein; CTX-I/-II, C-telopeptide of crosslinked collagen type I/II; CX3CL1, C-X3-C Motif Chemokine Ligand 1; ECM, extracellular matrix; EZH2, enhancer of zeste homolog 2, histone-lysine N-methyltransferase enzyme; HA, hyaluronic acid; HtrA1, high temperature requirement A family of homo-oligomeric and ATP-independent serine proteases; hsCRP, high sensitivity CRP; Hsp70, 70-kDa heat shock protein; iPTH, intermittent parathyroid hormone; LAR, leptin:adiponectin ratio; LNA043, modified human ANGPTL3; LOE, level of evidence based on AHRQ; M-CSF, macrophage colony-stimulating factor; MMP, matrix metalloproteinase; NF- κ B, nuclear factor kappa-light-chain-enhancer of activated B cells; NGF, nerve growth factor; N-MID, Osteocalcin; NO, nitric oxide; PDGF-BB, see rPDGF-BB; PGE₂, Prostaglandin E₂; PIIANP, N-propeptide of type IIA procollagen; PIIBNP, type IIB collagen NH₂-propeptide; PRO-C2, Type II Collagen Blood-Based Biomarker; RAGE, receptor for advanced glycation end products; ROR2 siRNA, receptor tyrosine kinase-like orphan receptor 2 small interfering ribonucleic acid; ROS, reactive oxygen species; rPDGF-BB, recombinant platelet-derived growth factor; Runx2, RUNX Family Transcription Factor 2; sCTX, serum CTX; SHOX, short stature homeobox; SNRI, Serotonin-norepinephrine reuptake inhibitors; SSNRI, Selective Serotonin Noradrenalin Reuptake Inhibitor; SSRI, selective serotonin reuptake inhibitors; TCA, Tricyclic Antidepressants; TG-2, transglutaminase-2; TKA, total knee arthroplasty; TREM-2, triggering receptor expressed on myeloid cells 2; TLR, Toll-like receptor; TPSB2, β -tryptase encoding gene; TrkB-Fc chimera, recombinant human neurotrophin receptor tyrosine kinase-Fc Chimera Protein; uALPHA-CTX, urinary ALPHA CTX; usCRP, ultra-sensitive CRP; uNTX-I, urinary N-telopeptide of type I collagen; VEGF, vascular endothelial growth factor; YKL-40, Chitinase 3-like 1. Explanations: bold and cursive terms/numbers, pain-related; Capsazepine, capsaicin receptor (TRPV1 (transient receptor potential cation channel, subfamily V, member 1)) antagonist; hypertrophic markers, markers of hypertrophic chondrocytes; Icatibant, selective/specific bradykinin B2 receptor antagonist; MEN16132, selective/specific bradykinin B2 receptor antagonist; Omalizumab, recombinant, humanized, monoclonal antibody against human immunoglobulin E; questioned = negative LOE, i.e., intervention without success OR lack of evidence according to current state of knowledge; Sprifermin, recombinant form of human fibroblast growth factor 18; Tanezumab, monoclonal antibody, completely humanized against NGF; TENS, transcutaneous electrical nerve stimulation; TMS, transcranial magnetic stimulation.

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