The Role of Bone in Osteoarthritis

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ACR Convergence
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Disclosures

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  - National Institutes of Health
- Consulting:
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  - BriOri Biotech, Theralogix LLC.

Off-label Drug Usage

- I will be discussing off-label use of the following medications:
  - BPs: Alendronate, risedronate, zoledronic acid
  - Calcitonin
  - Strontium ranelate

Evidence-based Medicine

- Thudium CS, et al: Bone phenotypes in rheumatology – there is more to bone than just bone. BMC Musculoskelet Disord 2020;21(1):789.
- Van Spil WE, et al: Osteoarthritis phenotypes and novel therapeutic targets. Biochem Pharmacol 2019;165:41-8.
- Bowes MA, Kacena K, Alabas OA, Brett AD, Dube B, Bodick N, Conaghan PG: Machine-learning, MRI bone shape and important clinical outcomes in osteoarthritis: data from the Osteoarthritis Initiative. Ann Rheum Dis 2020;80(4):502-8.

Oscar Gluck, MD
1949 - 2004

AMERICAN COLLEGE of RHEUMATOLOGY
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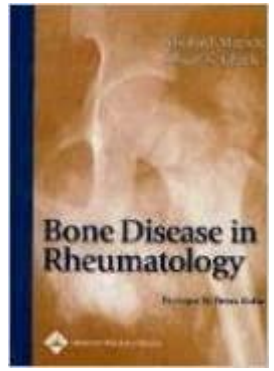
- Born and raised in Columbia
- Matriculated at University Del Valle, Cien de la Salud, Cali
- Residency at Barnes-Jewish Hospital, St. Louis, MO
- Fellowship at Washington University, St. Louis, MO
- Codirector, The Arizona Rheumatology Center, Pheonix, AZ
- Clinical Professor of Medicine, University of Arizona School of Medicine, Tucson, AZ
- Coeditor of “Bone Disease in Rheumatology”
  - Published posthumously by LWW in 2005



The Lord is My Shepherd
Psalm 23

Hashem is my Ro'eh (Shepherd); I shall not lack. He maketh me to lie down in green pastures; He leadeth me beside the mei menuchot (tranquil waters). He restoreth my nefesh; He guideth me in the paths of tzedek l'ma'an Shmo (righteousness for the sake of His Name). Yea, though I walk through the Gey Tzalmavet (Valley of the Shadow of Death), I will fear no rah (evil); for Thou art with me; Thy shevet (rod) and Thy staff they comfort me. Thou preparest a shulchan before me in the presence of mine enemies: Thou anointest my head with shemen (olive oil); my kos runneth over. Surely tov and chesed shall follow me kol y'mei chaiyyai (all the days of my life): and I will dwell in the Bais Hashem l'orech yamim (for length of days, whole life long, forever).

Painting by Thomas Hart Benton (1926), accessed at https://thomashartbenton.wordpress.com/tag/the-lord-is-my-shepherd/on 12 October 2021.

The term "Degenerative Joint Disease" is an anachronism and should never be used.

Osteoarthritis

- Osteoarthritis is a disorder involving movable joints characterized by cell stress and extracellular matrix degradation initiated by micro- and macro-injury that activates maladaptive repair responses including pro-inflammatory pathways of innate immunity. The disease manifests first as a molecular derangement (abnormal joint tissue metabolism) followed by anatomic and/or physiologic derangements (characterized by cartilage degradation, bone remodeling, osteophyte formation, joint inflammation and loss of normal joint function), that can culminate in illness.

https://oarsi.org/research/standardization-osteoarthritis-definitions. Accessed 05 October 2021.

Paleopathology and Osteoarthritis

- Paleopathology
  - The study of ancient diseases and injuries in organisms through the examination of fossils, mummified tissue and skeletal remains (skeletal paleopathology)
- Bony changes of OA, primarily eburnation and osteophytes, described in fossils of Neanderthal, Cro-Magnon and Paleolithic specimens as well as Egyptian mummies and skeletal specimens world-wide.

Dequeker J, Luyton F: Ann Rheum Dis 2008;67:6-10.

Paleopathology and Osteoarthritis among skeletons in England

- Classification of arthropathies in paleopathological specimens
  - Rogers J, et al: Ann Rheum Dis 1985;44(2):113-20.
  - Rogers J, et al: Arthritis Rheum 2004;50(2):452-7.
- OA is a disease that is primarily dependent on systemic predisposition to a particular type of bone response to mechanical stress.

Dieppe P, et al: Reumatismo 2006;58(2):79-84

Bone Pathology in OA

- Thickening of the tidemark layer of calcified cartilage
  - Breaching of the tidemark by sensory nerves growing through osteochondral channels
- Remodeling of the subchondral bone
  - Initial dysregulated activation of osteoclasts leading to bone resorption followed by increased bone formation with subchondral bone thickening with hypomineralized bone with altered material properties
- Osteophyte formation
  - Occurs at periphery of the joint from stem cells residing in periosteum under influence of growth factors (eg., TGF-B and BMP-2)
- Bone marrow lesions (BMLs)
  - Localized bone microdamage and remodeling/reparative changes

Reviewed by Ghadiali J, et al: In Hochberg MC, et al, eds. Rheumatology, 8e. Elsevier, Philadelphia, 2022, in press.

Pathologic Changes in OA

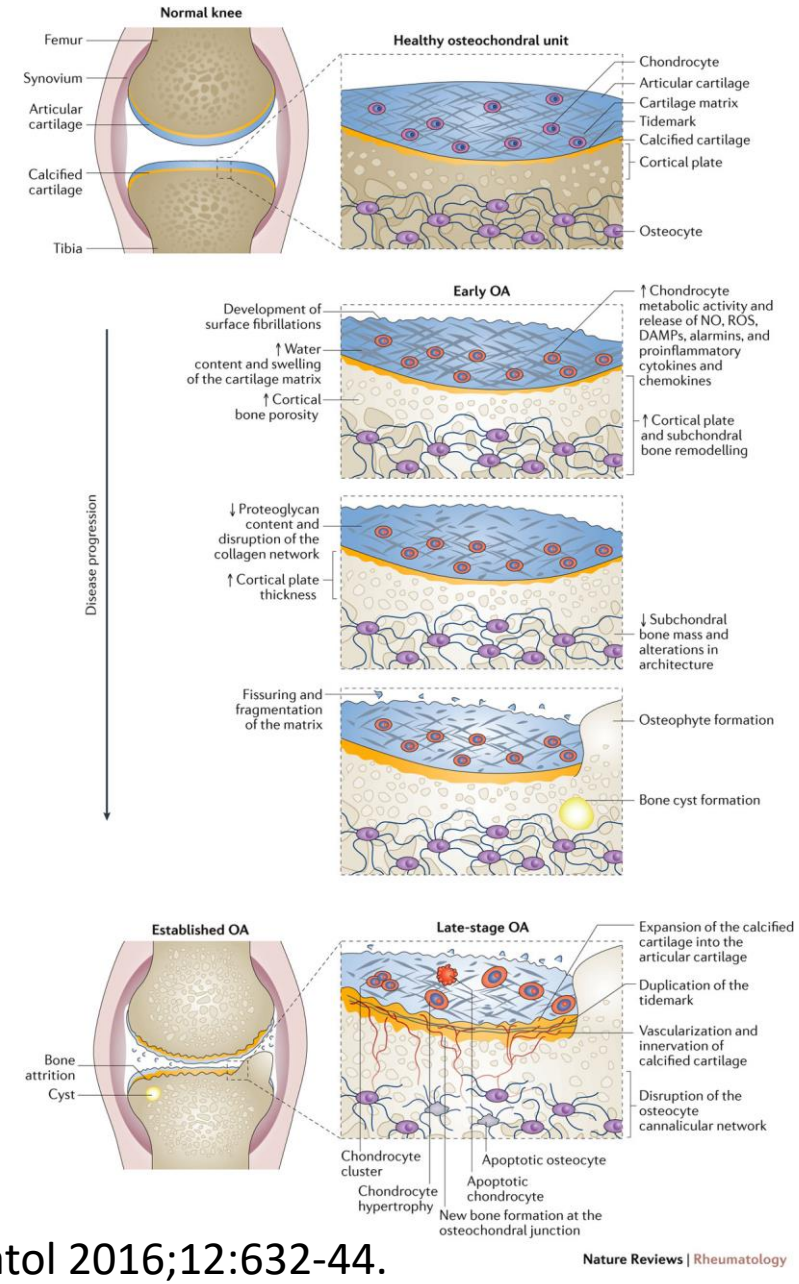
Table 1 | **Sequential changes in the osteochondral unit during the evolution of osteoarthritis**

Component of the osteochondral unit	Osteoarthritis-associated changes (in approximate sequential order for each component)
The cartilage matrix and chondrocytes	• Increase in water content with swelling of the cartilage matrix • Increase in chondrocyte anabolic and catabolic activity (including activity of MMPs, aggrecanases and other proteases) • Production of reactive oxygen species, nitric oxide, DAMPs, alarmins, and proinflammatory cytokines and chemokines • Decrease in proteoglycan content (decreased synthesis and increased breakdown) • Development of surface fibrillations • Disruption of the collagen network (increased breakdown) • Fissuring and fragmentation of the matrix • Chondrocyte apoptosis and development of chondrocyte clusters • Chondrocyte hypertrophy
Periarticular bone	• Increased cortical plate and subchondral cancellous bone remodelling • Increased cortical plate thickness (initially increased porosity and reduced stiffness with progression to increased cortical plate stiffness) • Decreased subchondral cancellous bone mass and alterations in architecture • Formation of osteophytes • Development of bone marrow lesions • Formation of bone cysts • Bone attrition (altered bone contour)
The calcified cartilage and osteochondral junction	• Penetration of the calcified cartilage by vascular channels with neural elements • Expansion of the zone of calcified cartilage with advancement into the articular cartilage • Duplication of the tidemark • New bone formation at the osteochondral junction

DAMPs, damage-associated molecular patterns; MMPs, matrix metalloproteinases.

Goldring SR, Goldring MB: Nat Rev Rheumatol 2016;12:632-44.

Structure of the normal knee joint and sequential changes in the osteochondral unit during the evolution of osteoarthritis



Goldring SR, Goldring MB: Nat Rev Rheumatol 2016;12:632-44.

The bone–cartilage unit is at the center of joint function and disease

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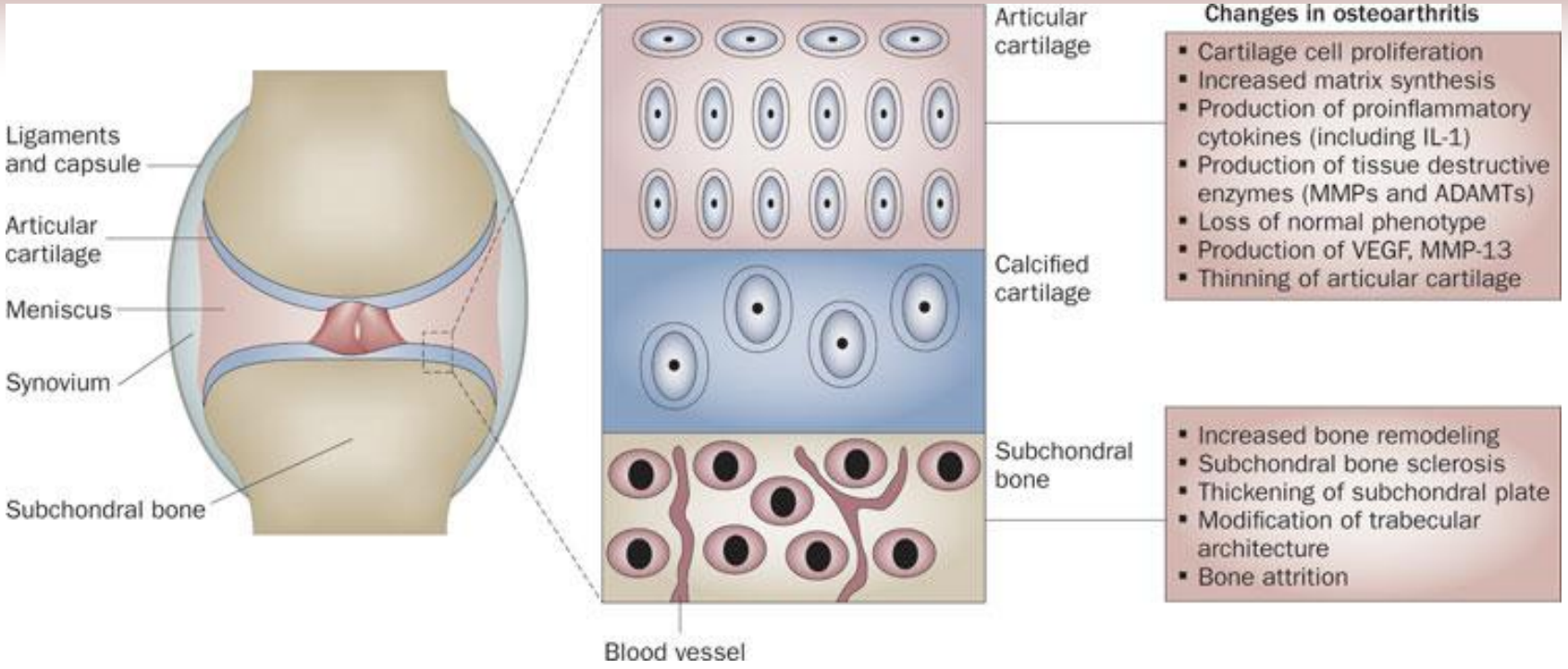


Lories, R. J. & Luyten, F. P. (2010) The bone–cartilage unit in osteoarthritis
Nat. Rev. Rheumatol. doi:10.1038/nrrheum.2010.197

nature REVIEWS RHEUMATOLOGY

Skeletal Genetic Disorders and Osteoarthritis

- Many inherited disorders of skeletal development can lead to the occurrence of OA in later life.
- 10th version of the Nosology committee of the International Skeletal Dysplasia Society classified 461 diseases into 42 groups based on the following criteria:
  - Genetic/molecular phenotypes
  - Radiographic criteria
  - Clinical phenotype
- Pathogenic variants affecting 437 different genes identified in over 90% of these disorders

Mortier GR, et al: Am J Med Genet A 2019;179(12):2393-419.

Hip Morphology and Hip Osteoarthritis

- Systematic review of observational studies in 6 databases through June 2020 with meta-analysis of 9 prospective studies to assess risk of developing incident and/or progressive hip OA
- Hip dysplasia, undercoverage of the acetabulum relative to the femoral head, defined as lateral center-edge angle (LCEA) <25^{o}
  - OR = 2.38 (95% CI: 1.84, 3.07)
- Cam-type morphology of femoroacetabular impingement (FAI), an aspherical femoral head defined as alpha angle >60^{o}
  - OR = 2.52 (95% CI: 1.83, 3.46)
- Pincer morphology of FAI, overcoverage of the acetabulum relative to the femoral head defined as LCEA >39^{o}
  - OR = 1.08 (95% CI: 0.57, 2.07)

Casartelli NC, et al: Osteoarthritis Cart 2021;29(9):1252-64.

Statistical Shape Modeling of the Hip and Hip Osteoarthritis

- Novel shape analysis technique that creates a set of shape modes in a standard population which can be used to examine variation in distribution of modes in disease
  - ASM toolkit (University of Manchester, UK) based on Procrustes analysis and Principal Component Analysis (PCA)
- Systematic review of observational studies in 5 databases through April 2020 with qualitative synthesis across 9 studies
- Total population of 4706 subjects with 6483 hips analyzed
  - Pooled mean age of 61.8 years; 69% were women

van Buuren MMA, et al: Osteoarthritis Cart 2021;29(5):607-18.

Statistical Shape Modeling of the Hip and Hip Osteoarthritis

- A total of 18 hip shape modes were associated with incident THR across 6 different studies
  - Shape modes consistent with Cam morphology (5 studies)
  - Shape modes consistent with acetabular dysplasia (4 studies)
- A total of 13 hip shape modes were associated with incident radiographic hip OA across 4 studies
  - Shape modes consistent with Cam morphology (2 studies)
  - Shape modes consistent with acetabular dysplasia (1 study)

van Buuren MMA, et al: Osteoarthritis Cart 2021;29(5):607-18.

Genome-wide Association Study of Novel Loci Associated with Hip Shape

- 10 hip shape modes derived by SSM using SHAPE software from hip DXA scans in 5 cohorts with available genotyping data (N = 15,934 of 19,379 subjects)
- A total of 9 SNPs at 8 loci were associated with 3 hip shape modes, several of these were associated with hip OA in arcOGEN study
- Most of the loci were close to genes involved in endochondral bone formation

Baird DA, et al: J Bone Miner Res 2019;34(2):241-51.

Statistical Shape Modeling of the Knee and Knee Osteoarthritis

- 13 distal femur and 10 proximal tibia shape modes accounted for ~95% of variance in shape in normal knee radiographs among persons enrolled in the OAI “incidence” subcohort
  - Shape differs by sex in persons without knee OA
- Specific shape modes were not associated with development of knee OA independent of sex
- Trajectories of change in shape differ by sex and presence of radiographic knee OA.

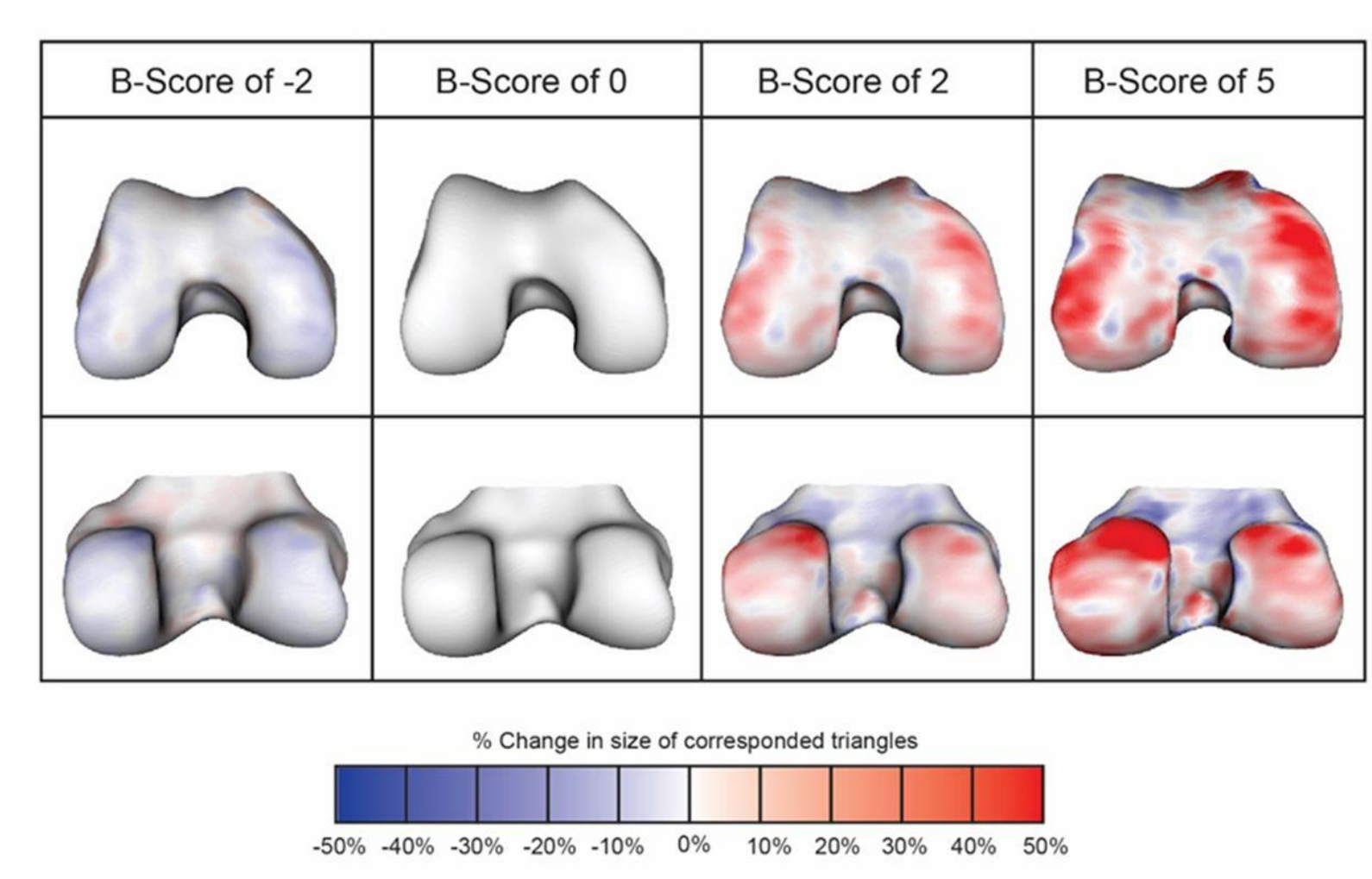
Wise BL, et al: Semin Arthritis Rheum 2016;46(1):20-6, BMC Musculoskelet Disord 2018;19(1):331 and Clin Orthop Relat Res 2020;478(7):1491-502.

MRI Bone Shape and Knee OA: Data from the OAI

- Statistical shape modeling MRI derived 3-D femur bone shape (B-score) measured from 9433 knee MRIs obtained at baseline
  - Femur shapes segmented from DESS-we images using active appearance models (AAMs) provided by Imorphics (Manchester, UK)
  - B-score = 0 defined as the mean shape for the sex-specific group with normal radiographs (KL grade 0) at each time point
- B-score had a non-linear association with KL grade at baseline
- B-score had a non-linear association with clinically important outcomes
- B-score discriminated within KL grade for pain and function

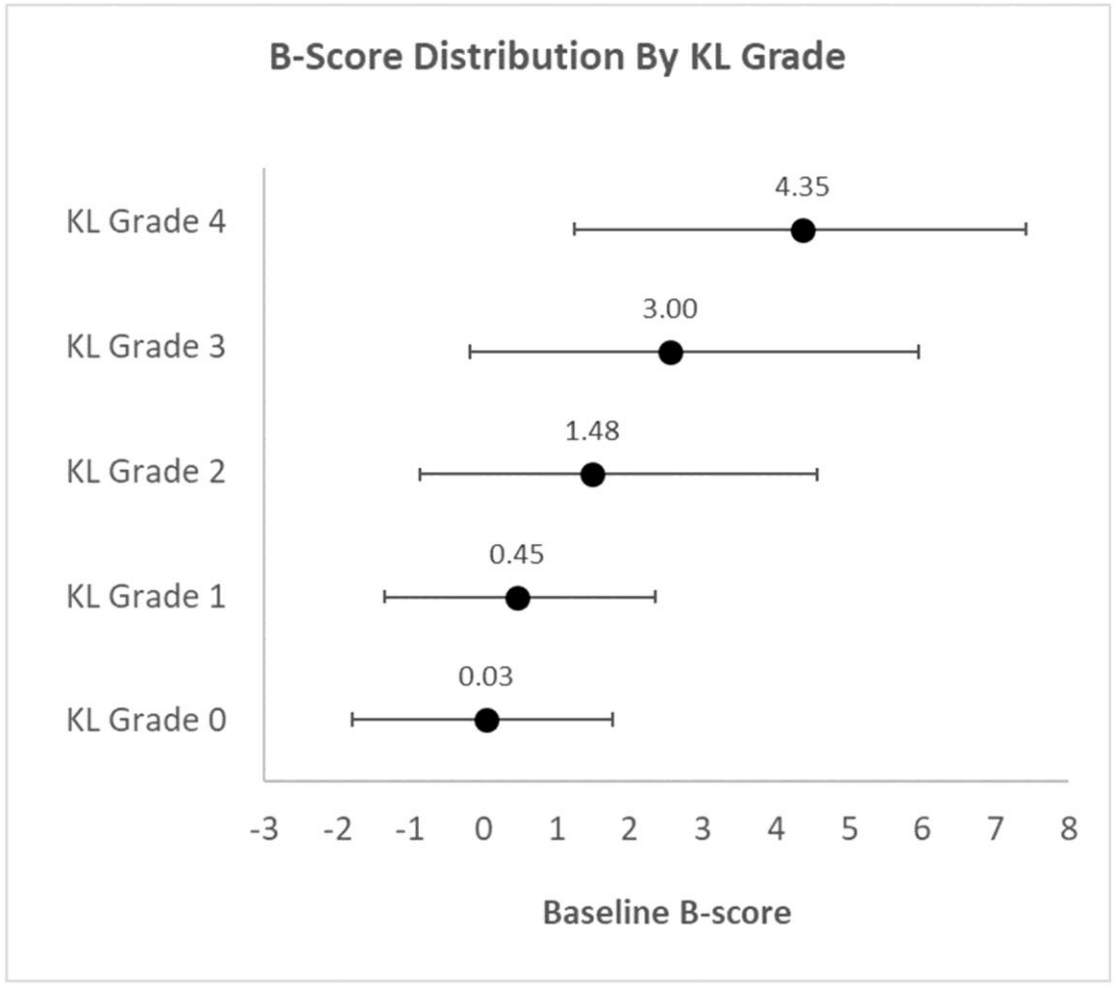
Bowes MA, et al: Ann Rheum Dis 2020;80(4):502-8..

Change in shape for the anterior femur (top row) and posterior femur (bottom row), for various B-scores.



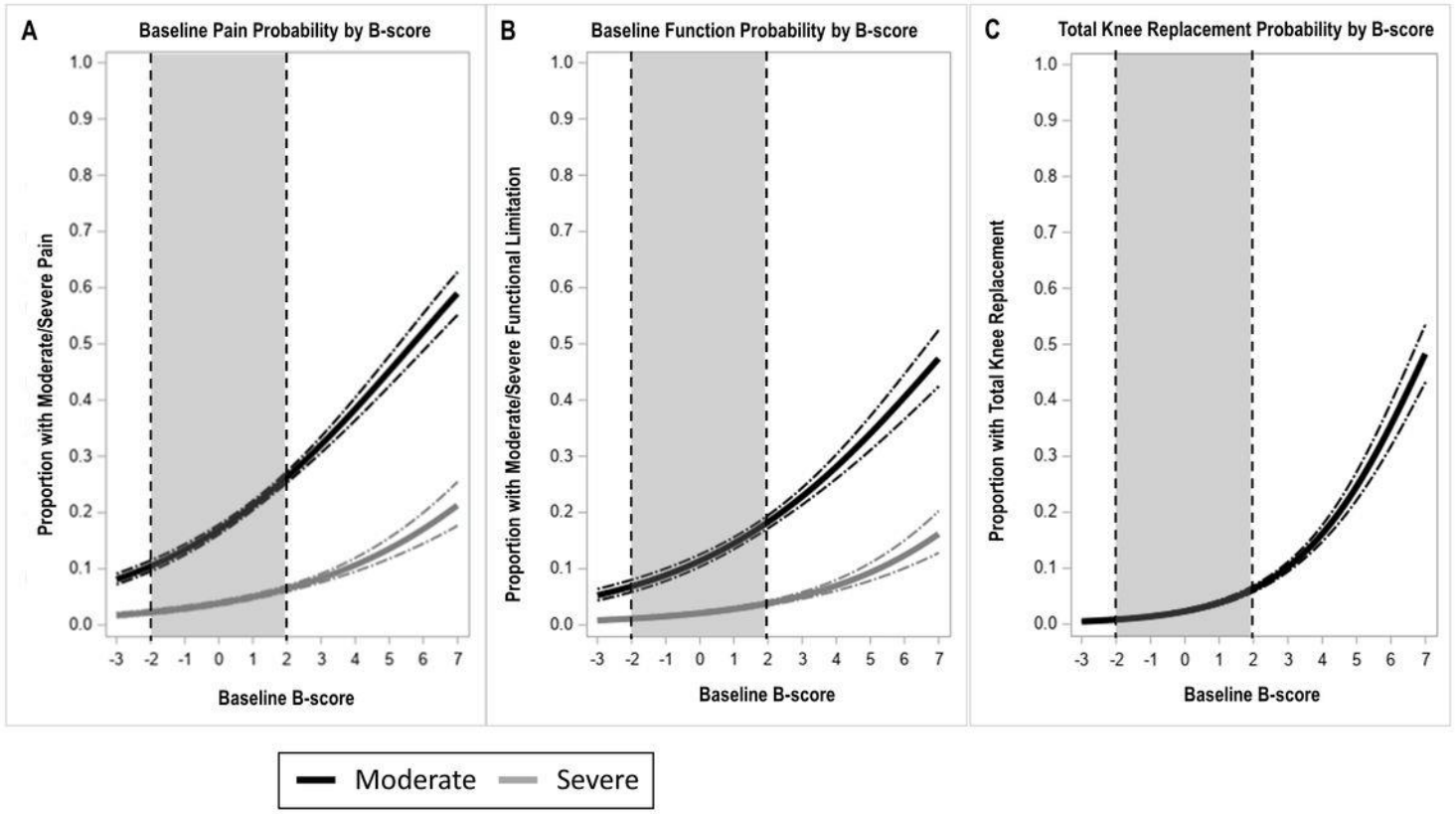
Michael A. Bowes et al. Ann Rheum Dis 2021;80:502-508

Distribution of B scores by KL grade are displayed for males and females (mean and 95% CIs for each grade).



Michael A. Bowes et al. Ann Rheum Dis 2021;80:502-508

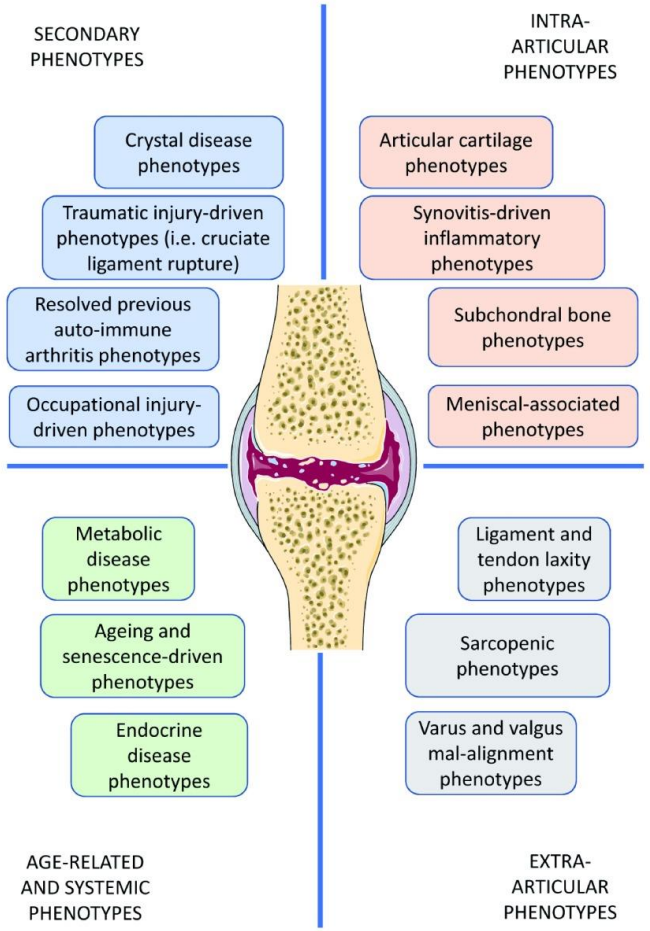
Clinically Important Outcomes Correlate with Increase in B-score



Michael A. Bowes et al. Ann Rheum Dis 2021;80:502-508

Phenotypes of Osteoarthritis

- OA is a heterogeneous and multifaceted disease with multiple molecular endotypes and clinical phenotypes
- Changes in subchondral bone as part of the osteochondral unit are pivotal in the mechano-adaptive phenotype



Mobasheri A, et al: F1000 Research 2019;8:2091 and Thudium CS, et al: BMC Musculoskel Dis 2020;21:789.

The High Bone Mass Phenotype in Osteoarthritis

- Foss and Byers compared percent cortical area of the 2nd metacarpal in 140 patients with hip fracture and 100 patients who had total hip arthroplasty for hip osteoarthrosis

Percent cortical area	Hip fracture men	Osteoarthritis men	Hip fracture women	Osteoarthritis women
> 90%ile	0 (0%)	15 (47%)	2 (1.7%)	36 (53%)
> 50%ile	5 (26.3%)	26 (81.3%)	29 (24%)	61 (89.7%)
< 50%ile	14 (73.7%)	6 (18.7%)	92 (76%)	7 (10.3%)
< 10%ile	12 (63%)	1 (3.1%)	51 (42%)	0 (0%)

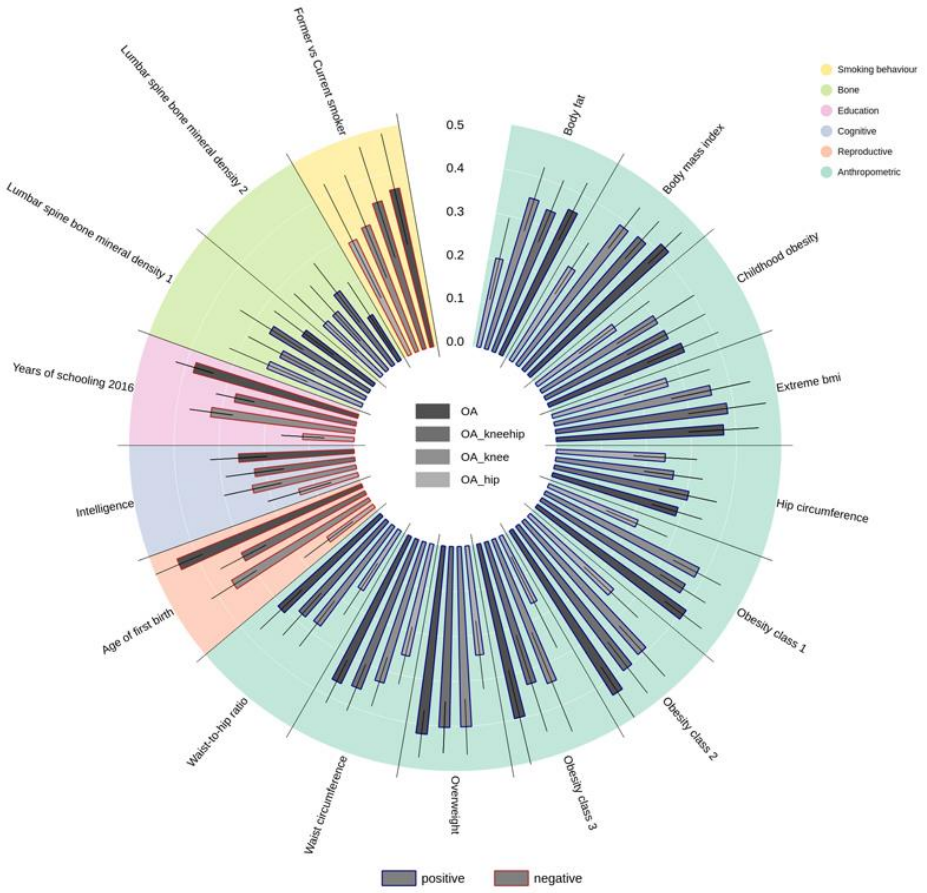
Foss MV, Byers PD: Ann Rheum Dis 1972;31(4):259-64.

The High Bone Mass Phenotype in Osteoarthritis

- Numerous cross-sectional studies have reported that persons with either hip or knee OA have higher bone mineral density than controls
- Numerous longitudinal studies have reported that higher bone mineral density was associated with development of hip and knee OA

Dequeker J, et al: Aging Clin Exp Res 2003;15(5):426-39, and Hochberg MC, Meyer JM: Osteoarthritis. In Maricic M and Gluck OS, eds. Bone Disease in Rheumatology. LWW, Philadelphia, 2005, 91-6.

Genetic correlations between OA and other traits



- GWAS for OA using data from UK Biobank and arcOGEN
  - 77,052 cases and 378,169 controls
- Identified 65 genome-wide significant variants (52 novel)
- LD-score analyses identified significant correlations with obesity and bone mineral density traits
- Strong enrichment for genes known to cause monogenic bone development disorders and forms of early-onset OA

Tachmazidou I, et al: Nat Genet 2019;51(2):230-6.

DNA Methylation Signatures of Bone Metabolism in OA

- Authors conducted a systematic review through February 2021 that identified articles concerning the association of DNA methylation signatures in age-related bone diseases
  - Non-English language articles, animal studies, case reports, abstracts, short communications and letters excluded
- Total of 96 publications served as basis for review
- DNA methylation patterns on OA examined in four tissues
  - Whole blood, cartilage, subchondral bone and synovium

Visconti VV, et al: Int J Mol Sci 2021;22(8):4244.

DNA Methylation Patterns in Subchondral Bone in OA

- Hip OA
  - EWAS in 12 patients identified 7316 differentially methylated CpG sites in subchondral bone underlying eroded cartilage
    - *TGFB3* highly hypermethylated and *EIF2C2* highly hypomethylated
    - *IGFBP7*, *LRP5*, *FTO* and *NCOR2* shared same methylation patterns in both subchondral bone and cartilage
      - Jeffries MA, et al: Arthritis Rheumatol 2016;68:1403-14
- Knee OA
  - EWAS in 12 patients identified differential methylated genes (DMGs) in different regions of the tibial plateau in early, mid and late-stage OA
    - DMGs differed between cartilage and bone and DMGs, including *TGFB3*, occurred earlier in subchondral bone than cartilage
      - Zhang Y, et al: Sci Rep 2016;6:34460

Visconti VV, et al: Int J Mol Sci 2021;22(8):4244.

Treatments of OA Focused on Bone Phenotype

Bisphosphonates for Treatment of Osteoarthritis: Preclinical Studies

- Systematic review of experimental studies of BPs for treatment of OA in animal models.
  - Studies published in English between 2000 and June 2020
  - Effects on biochemical markers and knee joint tissues
- 103 potential eligible papers identified and screened; 54 reviewed in full-text; 26 included in final review.
- Surgically induced models of OA in rabbits and rats (9 each), dogs and mice (3 each) and spontaneous OA in guinea pigs (2).
- Most common BPs studies were alendronate, zoledronic acid and risedronate.

Fernandez-Martin S, et al: Arthritis Res Ther 2021;23:60.

Bisphosphonates for Treatment of Osteoarthritis: Preclinical Studies

- Zoledronic acid showed the most consistent positive effects on chondroprotection, followed by alendronate and risedronate.
- Almost all studies exhibited greater periarticular bone conservation and quality as well as reductions in bone turnover markers.
- BPs did not inhibit the formation of osteophytes or synovial inflammation in most studies.
- Authors conclude that there is “a great heterogeneity in … outcomes” and “the evidence of their efficacy is poor …” but “further studies are needed in order to clarify their effectiveness.”

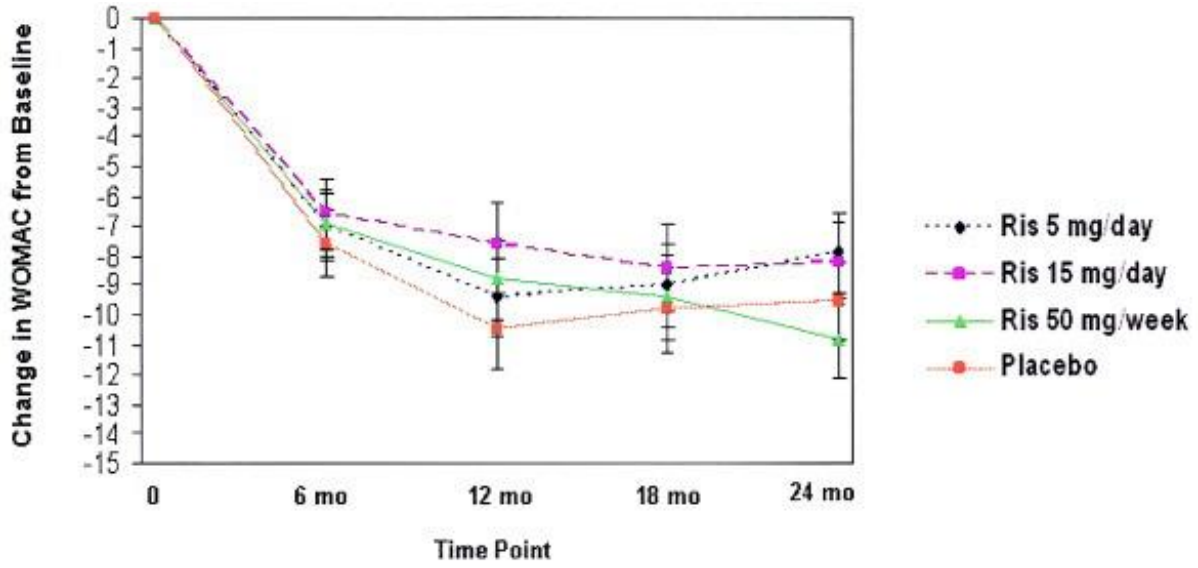
Fernandez-Martin S, et al: Arthritis Res Ther 2021;23:60.

Risedronate for Treatment of Knee OA: KOSTAR Trial

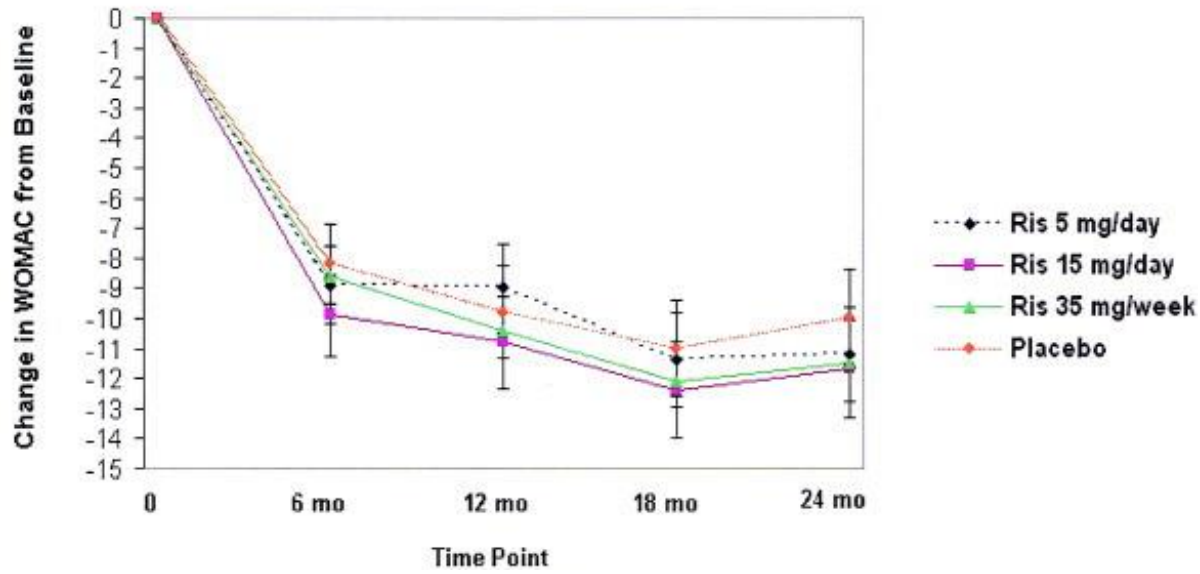
- Objective: Assess the efficacy of risedronate for symptom relief and slowing disease progression in patients with knee OA.
- Methods: Two parallel 2-year placebo-controlled RCTs conducted in NA and EU with multiple doses of risedronate.
- Participants: ACR classification criteria plus minimal joint space width of 2-4 mm in medial compartment.
- Co-primary outcomes:
  - Symptoms: WOMAC total score and PGA
  - Structure: Decline in joint space width in medial compartment

Bingham CO, et al: Arthritis Rheum 2006;3494-507.

North America



European Union



Risedronate for Treatment of Knee OA: KOSTAR Trial

- No significant differences in the proportion of patients with structural progression, defined as >= 0.6 mm, or the mean decline in medial joint space width between any risedronate dose group and placebo over 24 months.
- No differences between treatment groups in change in osteophyte worsening.
- Significant dose-dependent decline in urine levels of NTX-I and CTX-II reflecting reduction in bone and (calcified) cartilage turnover.

Bingham CO, et al: Arthritis Rheum 2006;3494-507.

Bisphosphonates for Treatment of Osteoarthritis: Systematic Review

- Systematic review of randomized controlled trials of BPs for treatment of OA.
  - Studies published in English between database inception to June 30, 2012
  - Primary outcome: effects on pain (WOMAC, VAS, VRS)
- 297 potential eligible papers identified and screened; 32 reviewed in full-text; 13 included in final qualitative synthesis.
- Most common BPs studies were risedronate and alendronate.
- Most common site of OA was the knee.

Davis AJ, et al: PLoS ONE 2013;8(9):e72714.

Bisphosphonates for Treatment of Osteoarthritis: Systematic Review

- Meta-analysis of oral risedronate studies
  - No significant difference in WOMAC pain or function outcomes with risedronate at varying doses (5 mg or 15 mg daily).
  - No significant difference in joint space narrowing or osteophyte formation during the 24-month follow-up.
  - Dose-dependent reduction in type-1 collagen N-telopeptide levels.
- Qualitative synthesis of mostly observational cohort studies
  - Limited evidence that BPs reduced pain, measured with VAS and WOMAC pain subscale, greater than placebo or non-treatment controls.
    - IV zoledronic acid significantly reduced VAS pain c/w IV saline at 6 but not 12 months; this was accompanied by a significant reduction in total area of BMLs at 6 but not 12 months. (Laslett LL, et al: Ann Rheum Dis 2012;71:1322-8).

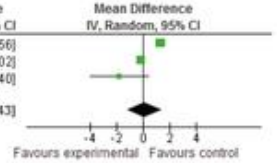
Davis AJ, et al: PLoS ONE 2013;8(9):e72714.

A. WOMAC pain

Risedronate 5 mg

Study or Subgroup	Biphosphonates Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Bingham 2006 EU 5mg	11.4	1.66	322	10.1	1.71	312	40.2%	1.30 [1.04, 1.56]
Bingham 2006 Nth Am. 5mg	8.2	1.39	306	8.4	1.34	310	40.4%	-0.20 [-0.42, 0.02]
Spector 2005 (5mg)	7	8	96	8.8	7.6	98	19.4%	-1.80 [-4.00, 0.40]
Total (95% CI)			724			720	100.0%	0.09 [-1.24, 1.43]

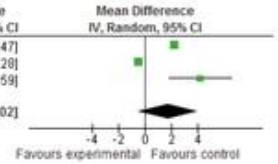
Heterogeneity: Tau² = 1.13; Chi² = 78.76, df = 2 (P < 0.00001); I² = 97%
Test for overall effect: Z = 0.14 (P = 0.89)



Risedronate 15 mg

Study or Subgroup	Biphosphonates Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Bingham 2006 EU 15mg	12.3	1.7	307	10.1	1.71	312	36.8%	2.20 [1.93, 2.47]
Bingham 2006 Nth Am 15mg	7.9	1.42	302	8.4	1.34	310	36.9%	-0.50 [-0.72, -0.28]
Spector 2005 (15mg)	13	9	90	8.8	7.6	98	26.4%	4.20 [1.81, 6.59]
Total (95% CI)			699			720	100.0%	1.73 [-0.56, 4.02]

Heterogeneity: Tau² = 3.69; Chi² = 242.01, df = 2 (P < 0.00001); I² = 99%
Test for overall effect: Z = 1.48 (P = 0.14)



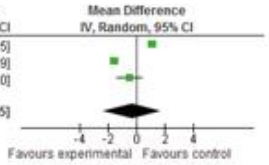
Bingham 2006 EU Risedronate 35 mg
Single item: Mean difference – 2.00 (95% CI: 1.73, 2.27)
Bingham 2006 Nth Am Risedronate 50 mg
Single item: Mean difference – 1.50 (95% CI: 1.29, 1.71)

B. Total WOMAC

Risedronate 5 mg

Study or Subgroup	Biphosphonates Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Bingham 2006 EU 5mg	11.2	1.58	322	10.1	1.63	312	33.9%	1.10 [0.85, 1.35]
Bingham 2006 Nth Am. 5mg	7.9	1.34	306	9.5	1.31	310	34.0%	-1.60 [-1.81, -1.39]
Spector 2005 (5mg)	8.5	3.2	96	9	3.2	98	32.1%	-0.50 [-1.40, 0.40]
Total (95% CI)			724			720	100.0%	-0.33 [-2.41, 1.75]

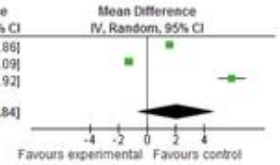
Heterogeneity: Tau² = 3.30; Chi² = 263.44, df = 2 (P < 0.00001); I² = 99%
Test for overall effect: Z = 0.31 (P = 0.76)



Risedronate 15 mg

Study or Subgroup	Biphosphonates Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Bingham 2006 EU 15mg	11.7	1.62	307	10.1	1.63	312	33.7%	1.60 [1.34, 1.86]
Bingham 2006 Nth Am 15mg	8.2	1.38	302	9.5	1.31	310	33.7%	-1.30 [-1.51, -1.09]
Spector 2005 (15mg)	15	3.2	90	9	3.2	98	32.6%	6.00 [5.08, 6.92]
Total (95% CI)			699			720	100.0%	2.06 [-0.73, 4.84]

Heterogeneity: Tau² = 5.99; Chi² = 456.78, df = 2 (P < 0.00001); I² = 100%
Test for overall effect: Z = 1.45 (P = 0.15)



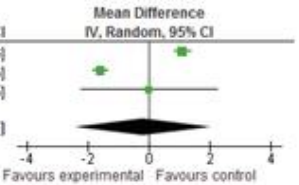
Bingham 2006 EU Risedronate 35 mg
Single item: Mean difference – 1.50 (95% CI: 1.25, 1.75)
Bingham 2006 Nth Am Risedronate 50 mg
Single item: Mean difference – 1.30 (95% CI: 1.09, 1.51)

A. WOMAC function

Risedronate 5 mg

Study or Subgroup	Biphosphonates Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Bingham 2006 EU 5mg	11	1.63	322	9.9	1.68	312	36.6%	1.10 [0.84, 1.36]
Bingham 2006 Nth Am. 5mg	7.7	1.65	306	9.3	1.33	310	36.6%	-1.60 [-1.84, -1.36]
Spector 2005 (5mg)	6	8	96	6	8	98	26.8%	0.00 [-2.25, 2.25]
Total (95% CI)			724			720	100.0%	-0.18 [-2.42, 2.06]

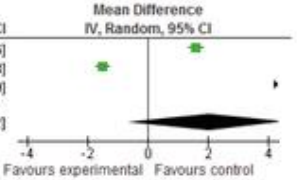
Heterogeneity: Tau² = 3.55; Chi² = 228.62, df = 2 (P < 0.00001); I² = 99%
Test for overall effect: Z = 0.16 (P = 0.87)



Risedronate 15 mg

Study or Subgroup	Biphosphonates Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Bingham 2006 EU 15mg	11.5	1.66	307	9.9	1.68	312	35.7%	1.60 [1.34, 1.86]
Bingham 2006 Nth Am 15mg	7.8	1.41	302	9.3	1.33	310	35.8%	-1.50 [-1.72, -1.28]
Spector 2005 (15mg)	13	8	90	6	8	98	28.5%	7.00 [4.71, 9.29]
Total (95% CI)			699			720	100.0%	2.03 [-0.66, 4.72]

Heterogeneity: Tau² = 5.27; Chi² = 355.30, df = 2 (P < 0.00001); I² = 99%
Test for overall effect: Z = 1.48 (P = 0.14)

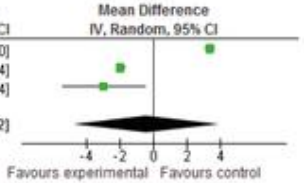


B. WOMAC stiffness

Risedronate 5 mg

Study or Subgroup	Biphosphonates Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Bingham 2006 EU 5mg	13.9	1.86	322	10.5	1.93	312	34.4%	3.40 [3.10, 3.70]
Bingham 2006 Nth Am. 5mg	9.9	1.65	306	11.9	1.59	310	34.5%	-2.00 [-2.26, -1.74]
Spector 2005 (5mg)	13	9	96	16	8.5	98	31.1%	-3.00 [-5.46, -0.54]
Total (95% CI)			724			720	100.0%	-0.45 [-4.82, 3.92]

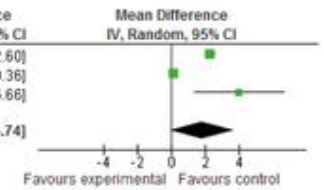
Heterogeneity: Tau² = 14.41; Chi² = 740.78, df = 2 (P < 0.00001); I² = 100%
Test for overall effect: Z = 0.20 (P = 0.84)



Risedronate 15 mg

Study or Subgroup	Biphosphonates Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Bingham 2006 EU 15mg	12.8	1.91	307	10.5	1.93	312	38.8%	2.30 [2.00, 2.60]
Bingham 2006 Nth Am 15mg	12	1.69	302	11.9	1.59	310	38.9%	0.10 [-0.16, 0.36]
Spector 2005 (15mg)	20	10	90	16	8.5	98	22.3%	4.00 [1.34, 6.66]
Total (95% CI)			699			720	100.0%	1.82 [-0.09, 3.74]

Heterogeneity: Tau² = 2.44; Chi² = 121.54, df = 2 (P < 0.00001); I² = 98%
Test for overall effect: Z = 1.87 (P = 0.06)



Davis AJ, Smith TO, Hing CB, Sofat N (2013) Are Bisphosphonates Effective in the Treatment of Osteoarthritis Pain? A Meta-Analysis and Systematic Review. PLOS ONE 8(9): e72714. https://doi.org/10.1371/journal.pone.0072714
https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0072714

Bisphosphonates for Treatment of Knee OA: Meta-analysis of RCTs

- Systematic review of placebo-controlled randomized controlled trials of BPs for treatment of knee OA.
  - Studies published between database inception to August 2017
  - Outcomes included effects on pain, function, radiographic progression and tolerability
- 201 potential eligible papers identified and screened; 15 reviewed in full-text; 7 included in final meta-analysis.
- Most common BP was oral risedronate.
- Methodologic quality low to moderate; however, no evidence of publication bias

Vaysbrot EE, et al: Osteoarthritis Cart 2018;26(2):154-64.

Bisphosphonates for Treatment of Knee OA: Meta-analysis of RCTs

- No significant difference in mean change in pain (6 trials), function (4 trials), or proportion experiencing radiographic progression at 24 months (2 trials) between BP and placebo.
- Results were robust to route of administration, duration of RCT and measurement scales for pain and function.
- Authors concluded that “BPs provide no significant benefit over placebo in patients with knee OA with regard to pain relief, functional improvement, or prevention of radiographic progression.”

Vaysbrot EE, et al: Osteoarthritis Cart 2018;26(2):154-64.

BPs as a Treatment Modality for Osteoarthritis: Narrative Review

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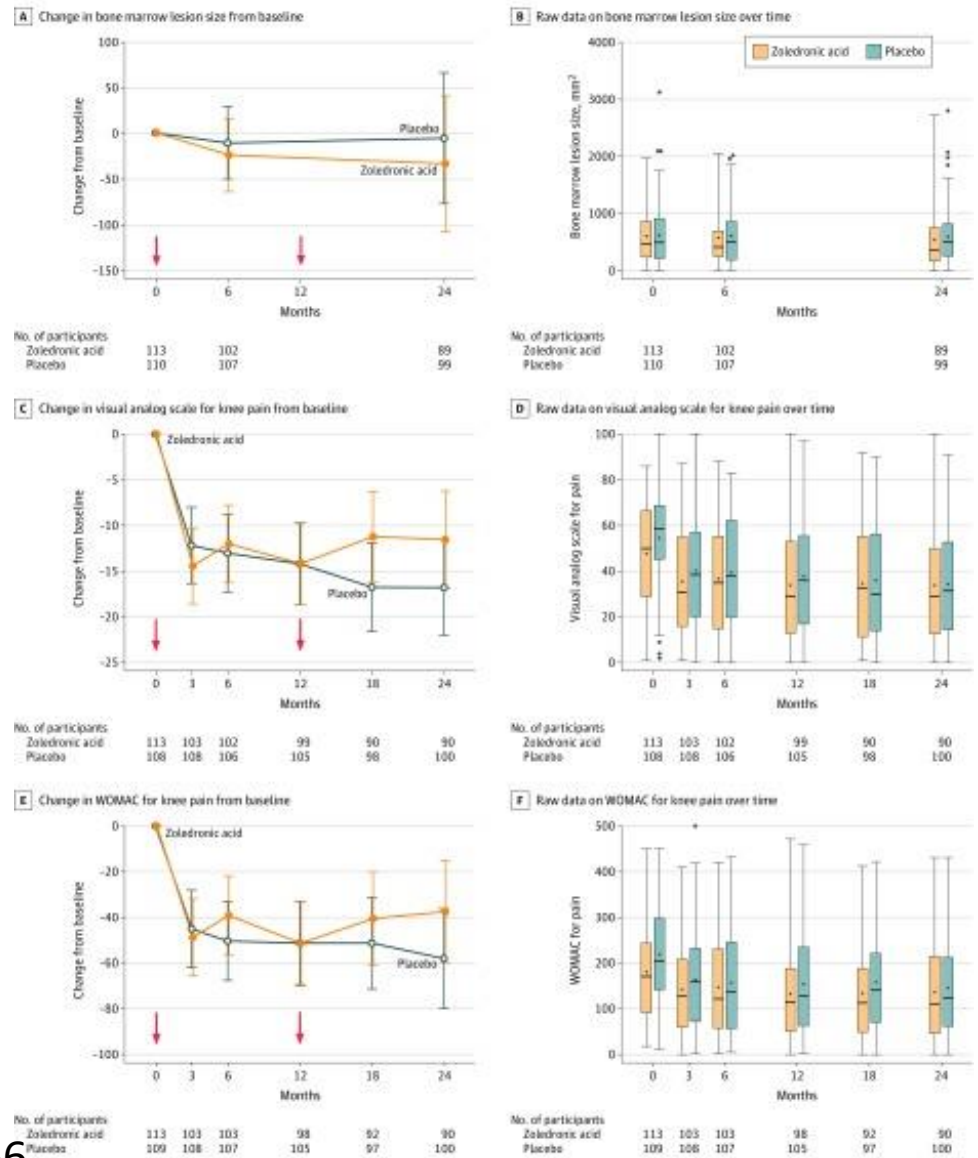
- Authors reviewed preclinical and human studies, including RCTs comparing BPs to placebo in patients with knee OA.
- "Evidence of symptomatic improvement and reduction of radiographic progression … was limited and inconclusive. However, reduced MRI BML size was demonstrated in two studies."
  - IV zoledronic acid reduced pain and BML area at 6 months c/w placebo
    - Laslett LL, et al: Ann Rheum Dis 2012;71(8):1322-8
  - IV zoledronic acid failed to reduce cartilage loss (change in tibiofemoral cartilage volume on qMRI), BML area or knee pain over 24 months
    - Cai G, et al: JAMA 2020;323(15):1456-66.

Eriksen EF, et al: Bone 2020. 115352.

Effect of IV ZA on Knee Pain and BML Size



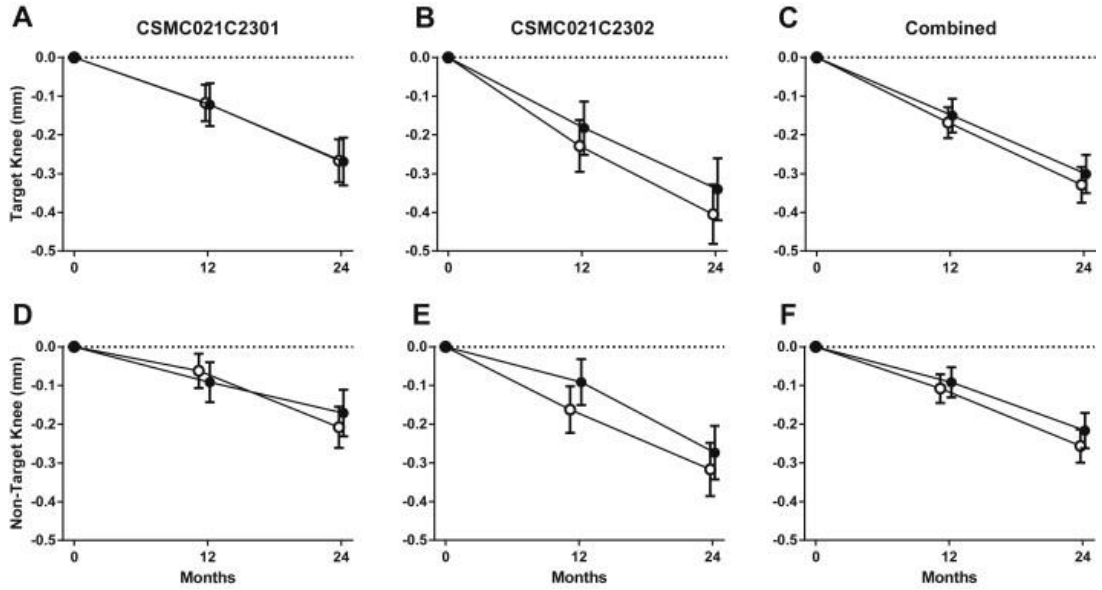
Cai G, et al: JAMA 2020;323(15):1456-66.

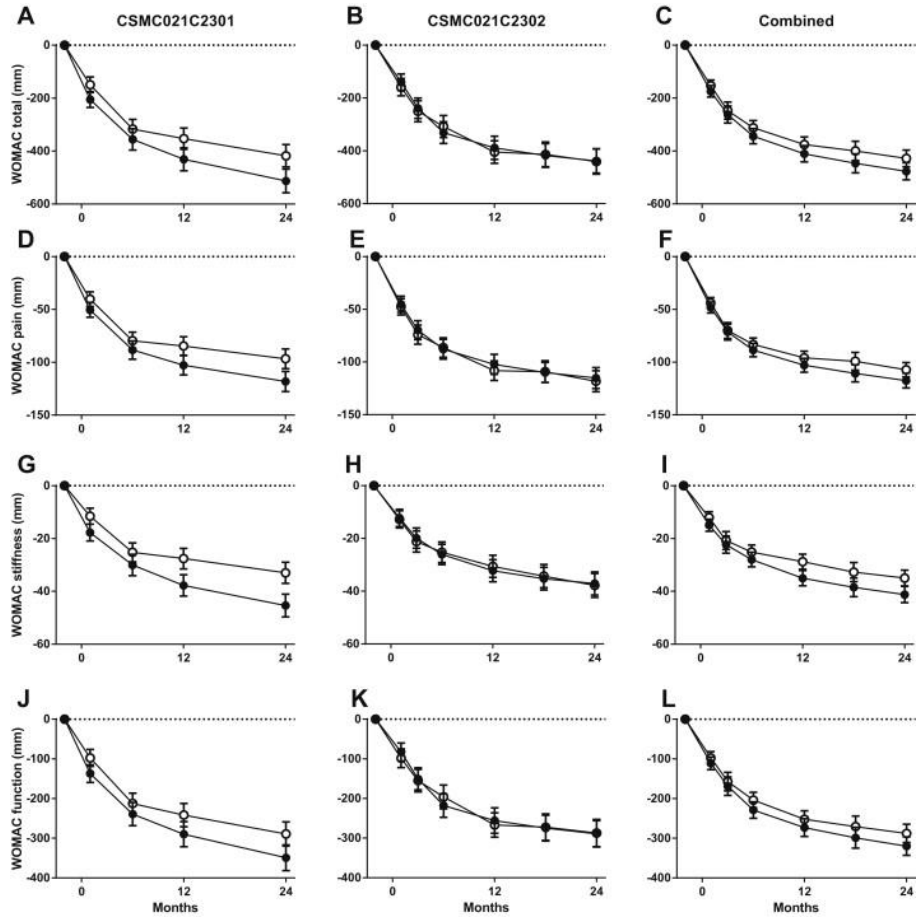
Oral Calcitonin for Treatment of Knee OA

- Objective: Assess the efficacy of oral salmon calcitonin for symptom relief and structure modification in knee OA.
- Methods: Two parallel 2-year placebo-controlled RCTs conducted in 11 countries with a single dose of calcitonin.
- Participants: ACR classification criteria plus minimal joint space width of 2 mm in medial compartment.
- Co-primary outcomes:
  - Structure: Decline in joint space width in medial compartment
  - Symptoms: WOMAC pain and function subscale scores

Karsdal MA, et al: Osteoarthritis Cart 2015;23(4):532-43.

Change in JSW and WOMAC scores over 24 months





Karsdal MA, et al: Osteoarthritis Cart 2015;23(4):532-43.

Oral Calcitonin for Treatment of Knee OA

- No significant treatment effect in either study of change in JSW at the 24-month study endpoint.
- One of two studies found a nominally significant effect on WOMAC pain and function at the 24-month study endpoint.
- There were numerical declines in urine levels of CTX-I and CTX-II and serum osteocalcin reflecting reduction in bone and (calcified) cartilage turnover.
- Higher incidence of adverse events (GI and hot flashes).

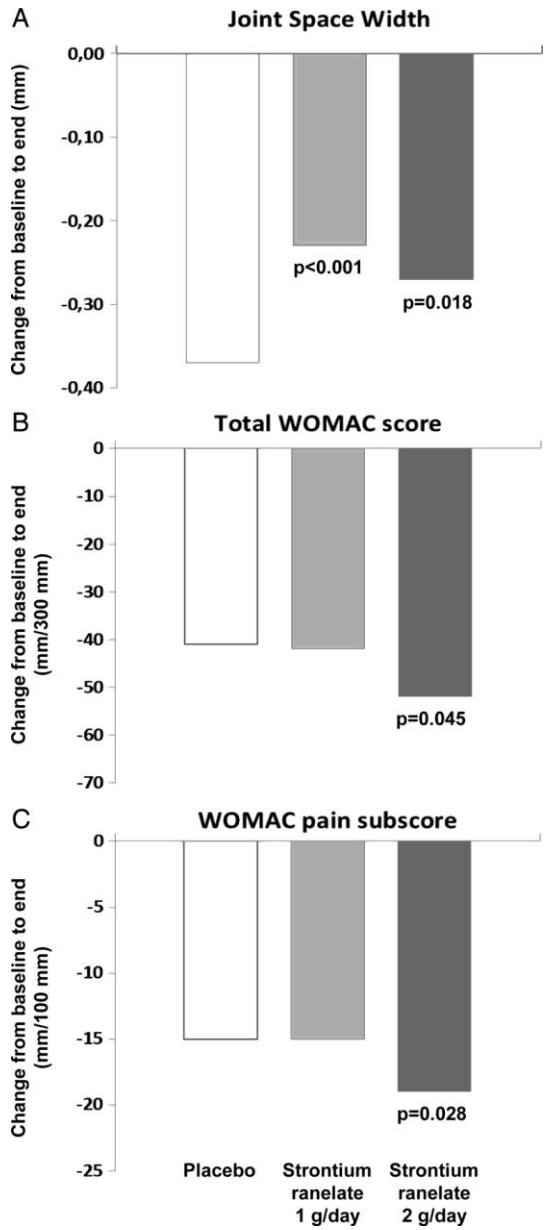
Karsdal MA, et al: Osteoarthritis Cart 2015;23(4):532-43.

Strontium Ranelate for Treatment of Knee OA

- Objective: Assess the efficacy of oral strontium ranelate for symptom relief and structure modification in knee OA.
- Methods: Randomized 3-year placebo-controlled RCT conducted in 18 countries with multiple doses of strontium.
- Participants: ACR classification criteria plus joint space width of 2.5-5 mm in medial compartment.
- Co-primary outcomes:
  - Structure: Decline in joint space width in medial compartment
  - Symptoms: WOMAC pain and function subscale scores

Reginster JY, et al: Ann Rheum Dis 2013;72(2):179-86 .

Effect of strontium ranelate on outcomes in knee osteoarthritis from baseline to end of study



Jean-Yves Reginster et al. Ann Rheum Dis 2013;72:179-186

Strontium Ranelate for Treatment of Knee OA

- Significant treatment effect of both doses of SR in change in JSW at the 36-month study endpoint.
- One of two doses of SR was associated with a significant effect on WOMAC total and pain score at the 36-month study endpoint.
- Lower percentage of radiographic (JSN >= 0.5mm) and radioclinical progessors (JSN >= 0.5mm and WOMAC pain <= 20%) at 36-months.
- There was significant decline in urine levels of CTX-II reflecting reduction in (calcified) cartilage turnover.

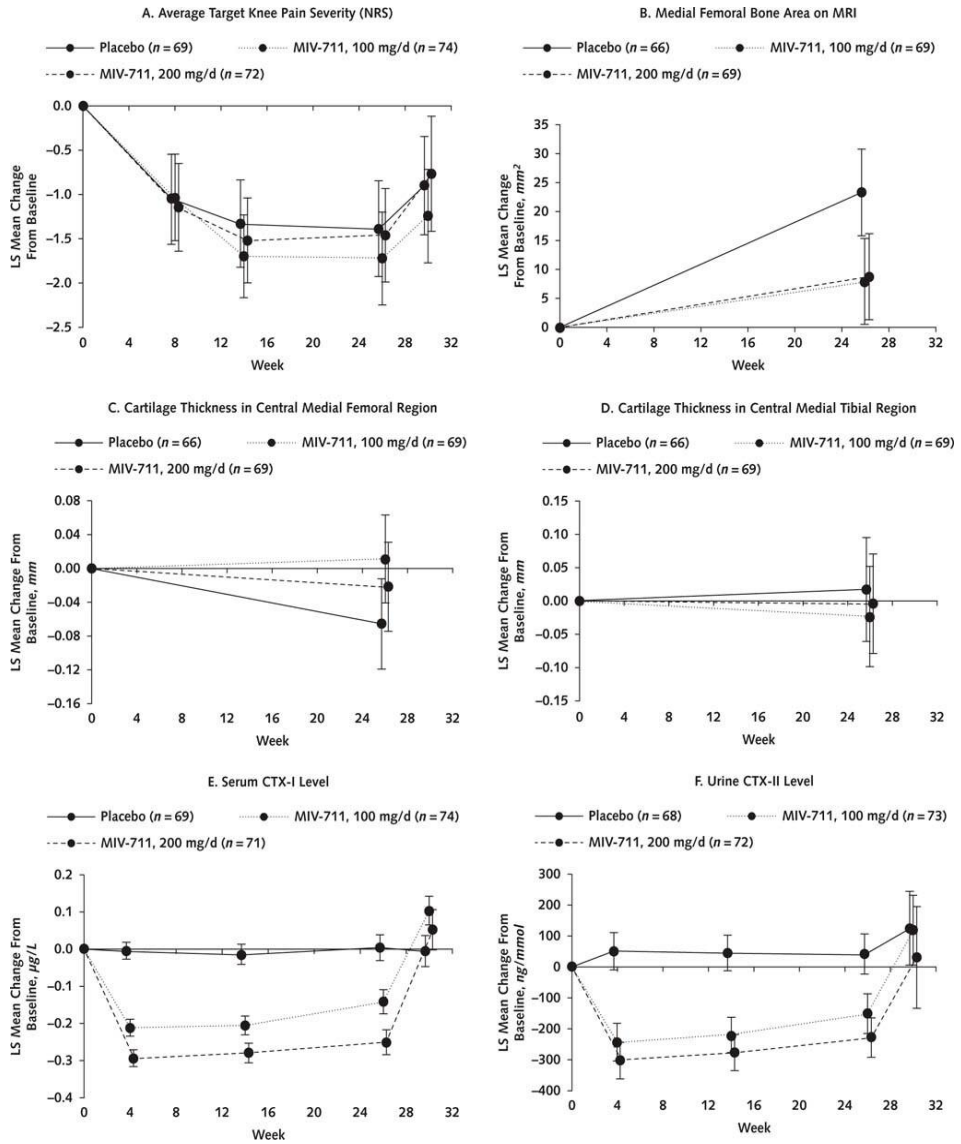
Reginster JY, et al: Ann Rheum Dis 2013;72(2):179-86 .

Cathepsin K Inhibitor for Treatment of Knee OA

- Objective: Assess the efficacy of a novel cathepsin K inhibitor for symptom relief and structure modification in knee OA.
- Methods: Randomized 26-week placebo-controlled phase 2a RCT conducted in 6 countries in EU with two doses of MIV-711.
- Participants: ACR classification criteria.
- Co-primary outcomes:
  - Symptoms: NRS pain score
  - Structure: Change in medial femoral bone area on MRI
  - Other secondary structure endpoints: Change in cartilage thickness and BML volume on MRI.

Conaghan PG, et al: Ann Intern Med 2020;172(2):86-95.

Estimated mean change from baseline in outcome by treatment group



Ann Intern Med. 2020; 172(2):86-95. doi:10.7326/M19-0675

Cathepsin K Inhibitor for Treatment of Knee OA

- No significant treatment effect of either dose of MIV-711 on change in NRS pain score at 26 weeks.
- Both doses of MIV-711 were associated with a significant effect on progression of medial femoral bone area as well as declines in serum levels of CTX-I and urine levels of CTX-II reflecting reductions in bone and (calcified) cartilage turnover.
- Lower dose of MIV-711 was associated with reduced decline in femoral cartilage thickness on MRI.
- MIV-711 was well tolerated.

Conaghan PG, et al: Ann Intern Med 2020;172(2):86-95.

Wnt Signaling Pathway and OA

- Family of glycoproteins involved in skeletal development and formation by promoting differentiation of mesenchymal cells towards osteoblasts and chondrocytes.
- Two main intracellular signaling pathways
  - Canonical via binding to frizzled receptors and LRP5/6 coreceptor
  - Non-canonical via binding to frizzled receptors and ROR2 coreceptor
- Excessive Wnt signaling leads to osteoarthritis
  - Frizzled-related protein (FRZB) polymorphisms associated with hip OA
  - Frzb knockout mice exhibit more cartilage damage in models of OA
- Absence of Wnt signaling also leads to osteoarthritis

Lories RJ, Monteagudo S: Rheumatol ther 2020;7(2):259-70.
Cherifi C, et al: Ther Adv Musculoskel Dis 2021;13:1-17.

Modulation of Wnt Signaling Pathway and OA

- Dickkopf-1 and sclerostin are both proteins that modulate Wnt signaling by binding to canonical receptors.
- High serum levels of Dickkopf-1 (Dkk1) are associated with reduced progression of radiographic hip OA
- Knockout of DKK-1 induced greater OA in rat model while overexpression in subchondral bone was beneficial for cartilage
- Deletion of sclerostin aggravated cartilage damage and subchondral bone remodeling in the DMM-model of OA in mice and ACL transection model of OA in mice, while overexpression protected against OA c/w wild-type mice

Lories RJ, Monteagudo S: Rheumatol ther 2020;7(2):259-70.
Cherifi C, et al: Ther Adv Musculoskel Dis 2021;13:1-17.

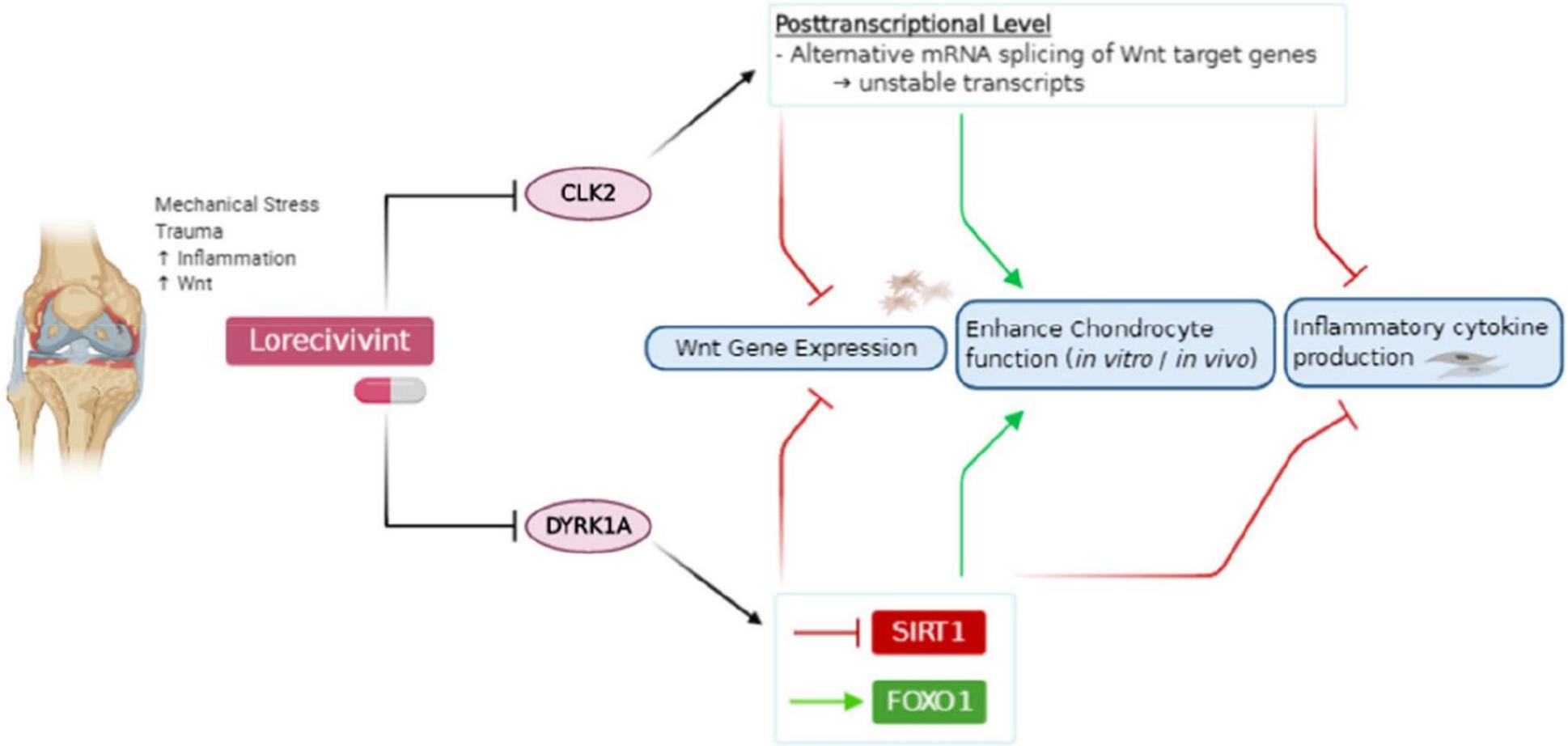


Figure 4. Proposed dual mechanism of action of lorecivivint. CLK2 inhibition causes alternative mRNA splicing at a posttranscriptional level, which leads to reduced expression of Wnt target genes and inflammatory cytokines. DYRK1 inhibition blocks SIRT1 (positive regulator of Wnt pathway) and promotes activation of FOXO1 (stimulates cartilage homeostasis), leading to negative regulation of Wnt signalling and direct chondroprotective effects. Green arrows indicate positive effects; closed red lines indicate inhibitory effects.

Lorecivivint

- Modulates Wnt signaling by inhibiting CDC-like kinase 2 and dual-specificity tyrosine phosphorylation-regulated kinase 1A
- Administered by intra-articular injection for knee OA
- Phase 1, 2A and 2B trials have been published
  - Yazici Y, et al: Osteoarthritis Cart 2017;25(10):1598-606.
  - Yazici Y, et al: Arthritis Rheumatol 2020;72(10):1694-706.
  - Yazici Y, et al: Osteoarthritis Cart 2021;29(5):654-66.
- Phase 3 trials currently in progress

Lane NE: Trans Am Clin Climatol Assoc 2020;131:55-64.
Sabha M, et al: Expert Opin Investig Drugs 2020;29(12):1339-46.

Summary

- Variations in bone shape contribute to the development of OA.
- Genetic control of the development of peak bone mass contributes to a “high bone mass” clinical phenotype in OA.
- Pathologic changes in bone are an integral component of the development and progression of osteoarthritis.
- Bone marrow lesions are associated with both pain as well as structural progression in OA.
- Treatments directed at altering bone turnover, however, have not been demonstrated convincingly to have efficacy for both structural progression or symptom relief in patients with knee OA.

Thank you and Acknowledgments

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- Roy D. Altman, MD
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- Co-editors of Rheumatology
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