La condroprotezione articolare nell'artrosi: nuove evidenze e linee guida terapeutiche

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Symptomatic slow acting drugs for OA (SYSADOA)

• Symptomatic slow acting drugs for OA (SYSADOA) have a slow onset of action but have additional benefits such as global efficacy similar to NSAIDs and a carry-over effect (the effect lasts for months even after treatment suppression).
• Moreover, these drugs have a high safety profile and the ratio cost/effectiveness is low.
• The main SYSADOAs are chondroitin sulfate (CS), glucosamine sulfate (GLU) and hyaluronic acid (HA). They are specially indicated in elderly patients, often polymedicated.
• SYSADOAs, apart from their symptomatic effect, also have a structure disease modifying effect slowing OA progression.
Recommendation for use of symptomatic slow-acting drugs for osteoarthritis (SYSADOAs) in the treatment of OA

<table>
<thead>
<tr>
<th>SySADOAs</th>
<th>Level of evidence or ES</th>
<th>Final recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>EULAR (2003)</td>
<td>Chondroitin sulfate and glucosamine sulfate</td>
<td>Recommended for symptomatic effect and might modify structure</td>
</tr>
<tr>
<td></td>
<td>Glucosamine sulfate</td>
<td>Recommended for OA symptoms</td>
</tr>
<tr>
<td></td>
<td>Glucosamine HCL</td>
<td>Not recommended</td>
</tr>
<tr>
<td>ACR (2012)</td>
<td>Chondroitin sulfate and glucosamine</td>
<td>Conditional recommendation NOT to use</td>
</tr>
<tr>
<td></td>
<td>Pain ES = 0.13 (0.00–0.27) to 0.75 (0.50–0.99)</td>
<td>Recommendation for disease modification: not appropriate</td>
</tr>
<tr>
<td></td>
<td>mJSW^a ES = 0.26 (0.14–0.38) to 0.30 (0.00–0.59)</td>
<td>Recommendation for symptom modification: uncertain</td>
</tr>
<tr>
<td></td>
<td>Glucosamine</td>
<td>Recommendation for disease modification: not appropriate</td>
</tr>
<tr>
<td></td>
<td>Pain ES = 0.17 (0.05–0.28) to 0.47 (0.23–0.72)</td>
<td>Recommendation for disease modification: not appropriate</td>
</tr>
<tr>
<td></td>
<td>mJSW^a ES = 1st year: 0.08 (−0.12 to 0.27); 3rd year: 0.43 (0.24–0.63)</td>
<td>Recommendation as a background treatment in the initial pharmacological management</td>
</tr>
<tr>
<td>ESCEO (2014)</td>
<td>Glucosamine sulfate</td>
<td>Recommended as a background treatment in the initial pharmacological management</td>
</tr>
<tr>
<td></td>
<td>Chondroitin sulfate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pain ES from mild to moderate</td>
<td></td>
</tr>
</tbody>
</table>
Is there any scientific evidence for the use of glucosamine in the management of human osteoarthritis?

Yves Henrotin, Ali Mobasher and Marc Marty

Arthritis Research & Therapy 2012, 14:201

**GLUCOSAMINE SULFATE ACTION MECHANISMS**

**STIMULATES:**
- ↑ proteoglycans

**EFFECT:**
- Anti-inflammatory activity
- Membrane stabilising activity

**INHIBITS:**
- cartilage degradative enzymes (collagenase, aggrecanase, phospholipase A2, etc.)
- MMP-3, MMP-2, MMP-9
- free radicals
- PGE2
- IL-1
- NF-kB
Both glucosamine (GlcN) and diacerein promoted a differentiated chondrocytic phenotype of immortalized human C-28/I2 chondrocytes by altering proliferation, morphology, and collagen type I COL2/COL1 mRNA ratios. Moreover, both agents antagonized inhibitory effects of IL-1β by enhancing aggrecan and COL2 as well as by reducing COL1 mRNA levels.
The Effects of Glucosamine Hydrochloride on Subchondral Bone Changes in an Animal Model of Osteoarthritis

Susanne X. Wang,1 Sheila Laverty,2 Mircea Dumitriu,1 Anna Plaas,3 and Marc D. Grynpas1

This study shows that subchondral bone turnover, structure, and mineralization are significantly altered in the early stages of experimental OA, and that these changes are attenuated by glucosamine treatment.

ARTHritis & RHEumatism
Vol. 56, No. 5, May 2007, pp 1537–1548
Serum cartilage oligomeric matrix protein (COMP) decreased significantly over the 12-week training period when treatment with glucosamine. This suggests an effect by glucosamine on the response of the OA cartilage to a period of joint loading in humans with knee OA.
Both glucosamine sulfate and chondroitin are safe medications, with no difference in adverse effects compared with placebo, which would also strengthen their role as chronic background treatments.
The findings of this study indicate that glucosamine sulfate at the oral once-daily dosage of 1,500 mg is more effective than placebo in treating knee OA symptoms.
Combined chondroitin sulfate and glucosamine for painful knee osteoarthritis: a multicentre, randomised, double-blind, non-inferiority trial versus celecoxib


Marc C Hochberg,1 Johanne Martel-Pelletier,2 Jordi Monfort,3,4 Ingrid Möller,5 Juan Ramón Castillo,6 Nigel Arden,7,8,9 Francis Berenbaum,10 Francisco J Blanco,11 Philip G Conaghan,12 Gema Doménech,13 Yves Henrotin,14,15 Thomas Pap,16 Pascal Richette,17,18 Allen Sawitzke,19 Patrick du Souich,20 Jean-Pierre Pelletier,2 on behalf of the MOVES Investigation Group

Chondroitin sulfate plus glucosamine hydrochloride (CS+GH) has comparable efficacy to celecoxib in reducing pain, stiffness, functional limitation and joint swelling/effusion after 6 months in patients with painful knee osteoarthritis, with a good safety profile.
Efficacy and safety of glucosamine sulfate in the management of osteoarthritis: Evidence from real-life setting trials and surveys

Olivier Bruyère, PhD\textsuperscript{a,*}, Roy D. Altman, MD\textsuperscript{b}, Jean-Yves Reginster, MD, PhD\textsuperscript{c}

<table>
<thead>
<tr>
<th>Study</th>
<th>WOMAC Pain</th>
<th>WOMAC Function</th>
<th>Lequesne Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reginster, 3 yrs (Lancet 2001)</td>
<td>0.27 (0.00 to 0.54)</td>
<td>0.32 (0.05 to 0.59)</td>
<td>0.44 (0.16 to 0.72)</td>
</tr>
<tr>
<td>Pavelka, 3 yrs (Arch Int Med 2002)</td>
<td>0.30 (0.03 to 0.58)</td>
<td>0.32 (0.04 to 0.60)</td>
<td>0.32 (0.05 to 0.59)</td>
</tr>
<tr>
<td>Herrero (GUIDE), 6 mths (Arthritis Rheum 2007)</td>
<td>0.25 (-0.03 to 0.52)</td>
<td>0.34 (0.07 to 0.61)</td>
<td>0.38 (0.18 to 0.57)</td>
</tr>
<tr>
<td>POOLED</td>
<td>0.27 (0.12 to 0.43)</td>
<td>0.33 (0.17 to 0.48)</td>
<td>0.38 (0.18 to 0.57)</td>
</tr>
</tbody>
</table>

Seminars in Arthritis and Rheumatism 45 (2016) S12–S17
Structural and Symptomatic Efficacy of Glucosamine and Chondroitin in Knee Osteoarthritis

A Comprehensive Meta-analysis

Florent Richy, MSc; Olivier Bruyere, MSc; Olivier Ethgen, MSc; Michel Cucherat, MSc, PhD; Yves Henrotin, MSc, PhD; Jean-Yves Reginster, MD, PhD

Arch Intern Med. 2003;163:1514-1522

Figure 2. Effect sizes of symptomatic outcomes. LI indicates Lequesne Index; WOMAC, Western Ontario MacMaster University Osteoarthritis Index; and VAS, visual analog scale.
Compared to placebo, glucosamine showed a significant improvement with unstandardized mean differences in total WOMAC, pain WOMAC, function WOMAC, and Lequesne score.
The Pharmaco-Epidemiology of GonArthroSis (PEGASus) was a cohort study of continuous recruitment of patients with “dynamic” exposure to the investigated SYSADOA (crystalline glucosamine sulfate, glucosamine hydrochloride, chondroitin sulfate, diacerein, and avocado–soybean unsaponifiables, all at approved dosages).

Crystalline glucosamine sulfate was the only SYSADOA that decreased the use of NSAIDs in this study in patients with knee OA.
The objective of this study was glucosamine sulfate versus combination of glucosamine sulfate and Non-Steroidal anti inflammatory drugs (NSAID) in mild to moderate knee osteoarthritis.

Study results may suggest that the Glucosamine Sulfate has a carryover effect like Disease-modifying agents. Long-term treatment of Glucosamine Sulfate may reduce the dependence of NSAIDs usage and delay the disease progression. Thereby we can reduce the NSAIDs side effects and improve the patient’s quality of life.
Mean costs associated with use of OA medication and OA-related healthcare resources per patient per year among OA patients who had received patented crystalline glucosamine sulfate (pCGS) 5 years previously versus placebo.
Conventional medical therapy for osteoarthritis: current state of the evidence

Allan C. Gelber

From the NIH Osteoarthritis Initiative, we learn that a combination of glucosamine and chondroitin was associated with a structural benefit to the knee, though we are not informed about the dose of glucosamine and chondroitin consumed, the formulation used, or the compliance rate with the supplement.
Evidence for a disease-modifying effect of patented crystalline glucosamine sulfate (pCGS): prevention of joint space narrowing in knee osteoarthritis

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 106)</th>
<th>pCGS (n = 106)</th>
<th>Difference</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reginster et al. [24]</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>JSW at enrollment, mm (mean ± SD)</strong></td>
<td>3.95 ± 1.24</td>
<td>3.82 ± 1.32</td>
<td>- 0.13</td>
<td>-</td>
</tr>
<tr>
<td><strong>3-year JSN, mm (mean and 95% CI)</strong></td>
<td>-0.40 (-0.56 to -0.24)</td>
<td>-0.07 (-0.22 to 0.07)</td>
<td>0.33 (0.12–0.54)</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>Pavelka et al. [25]</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>JSW at enrollment, mm (mean ± SD)</strong></td>
<td>3.63 ± 1.57</td>
<td>3.89 ± 1.48</td>
<td>- 0.26</td>
<td>-</td>
</tr>
<tr>
<td><strong>3-year JSN, mm (mean and 95% CI)</strong></td>
<td>-0.19 (-0.29 to -0.09)</td>
<td>0.04 (-0.06 to 0.14)</td>
<td>0.23 (0.09–0.37)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

CI, confidence interval; JSN, joint space narrowing; JSW, joint space width; pCGS, patented crystalline glucosamine sulfate; SD, standard deviation.
Allocation to the glucosamine–chondroitin combination resulted in a statistically significant reduction in JSN at 2 years.
A 24-month, double-blind, placebo-controlled study, conducted at 9 sites in the United States as part of the Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT), enrolled 572 patients with knee OA treatment effects on K/L grade 2 knees, but not on K/L grade 3 knees, showed a trend toward improvement relative to the placebo group.

Knees with K/L grade 2 radiographic OA appeared to have the greatest potential for modification by these treatments.
Glucosamine sulfate decreased the risk of developing radiographic knee OA over 2.5 years in overweight, middle-aged women at risk, as determined by medial mJSN progression.
Real-life patient cohort follow-up studies have demonstrated that the structure-modifying effects of pCGS appear to translate into clinically relevant benefits in knee OA, i.e., a delay in the need for total joint replacement.
Only patented crystalline glucosamine sulfate (pCGS). Only pCGS is given as a highly bioavailable once-daily dose (1.500 mg) with a proven pharmacological effect that equates to a clear clinical benefit in trials and real-life studies of knee OA.
An algorithm recommendation for the management of knee osteoarthritis in Europe and internationally: A report from a task force of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO)

**BASIC PRINCIPLE AND CORE SET**

- Combination of treatment modalities, including non-pharmacological and pharmacological therapies is strongly recommended
- Core set: Information/Education
  - Weight loss if overweight
  - Exercise program (aerobic, strengthening)

**STEP 1: Background treatment**

- **if symptomatic**
  - (Paracetamol on a regular basis)
  - OR
  - Chronic SYSADOA: prescription glucosamine sulfate and/or chondroitin sulfate ± as needed paracetamol

  - **if still symptomatic ADD**
    - Topical NSAIDs (OR)
    - (Topical capsaicin)

- **Referral to physical therapist for:**
  - if needed (to control malalignment)
    - Knee braces
    - (Insoles)

- **if symptomatic ADDITION at any time**
  - Walking aids
  - Thermal agents
  - Manual therapy
  - Patellar taping
  - Chinese acupuncture
  - TENS
Difficulties with assessing the benefit of glucosamine sulphate as a treatment for osteoarthritis

Nikki Burdett MBBS and Julian David McNeil MBBS FRACP FRCP PhD

*Int J Evid Based Healthc* 2012; **10**: 222–226

Abstract

Osteoarthritis is a chronic disease with a major impact on quality of life for a large proportion of the population. It is a disease for which to date there has been no disease-modifying therapy identified. As a result of its physiological role in articular cartilage, glucosamine sulphate has been postulated as a treatment for osteoarthritis. Claims have included symptomatic relief and even reduction in the rate of disease progression. Despite promising *in vitro* studies, however, the role of glucosamine sulphate in the management of osteoarthritis remains unclear. Studies addressing this issue have generated a wide range of conclusions, and these are discussed here. Methodological issues need to be addressed in order to gauge whether there is true benefit. On current evidence, it would appear that the benefits of dietary supplementation with glucosamine sulphate are limited to mild symptomatic relief, while a disease-modifying agent for this disease remains elusive.
OA IN THE PAST

A disease of cartilage and bone

RADIOGRAPHS

RADIOGRAPHIC CHANGES:
- OSTEOPHYTES
- JOINT SPACE NARROWING
- SCLEROSIS
- SUBCHONDRAL CYSTS

Conventional radiographs
Imaging of cartilage and bone: promises and pitfalls in clinical trials of osteoarthritis

Osteoarthritis and Cartilage 22 (2014) 1516–1532

F. Eckstein † ‡ *, A. Guermazi § ¶, G. Gold ¶, J. Duryea #, M.-P. Hellio Le Graverand † ‡, W. Wirth † ‡, C.G. Miller ¶ ¶

Radiography

- Standards of knee positioning (weight-bearing and fixed flexion) are important.
- Each of both knees should be imaged separately to ensure minimal X-ray beam divergence.
- The X-ray beam must be aligned with the medial tibial plateau; the IMD should be ≤1.0 mm.
- Several modifications of radiographic classification systems exist, these should therefore be clearly defined and documented.
- In fixed flexion radiographs of OA knees, central fixed location JSW measurements may be more responsive than that of minimum JSW.
Effetti della variazione dell’ angolo femoro-tibiale sulla valutazione dell’ ampiezza della rima articolare e dello spessore della cartilagine articolare.

Apparente assottigliamento della cartilagine e riduzione della rima articolare in corrispondenza della parte posteriore del condilo femorale (freccia blu) in caso di posizionamento del paziente con ginocchio in semi-flessione (B), rispetto all’ immagine ottenuta con il ginocchio in completa estensione (A).
OA IN THE PRESENT

A whole joint disease

MRI

ARTHROSCOPY ULTRASOUND

PRE-RADIOGRAPHIC STRUCTURAL TISSUE CHANGES:
- CARTILAGE DEFECTS
- MENISCUS LESIONS
- BONE MARROW LESIONS
- SYNOVITIS

EARLIER DIAGNOSIS OF OA
Stages of OA incorporating the new taxonomy. Three stages can be imagined: a no disease/no illness stage, a subclinical stage (with disease manifestations only) and a clinical stage (with illness manifestations).
The tissue functional threshold for establishment of a clinical symptomatic disease differs by organ system. The horizontal dashed lines depict the transition from disease to illness for different diseases. The threshold is relatively high in heart, liver and kidney disease but anticipated to be relatively low for the transition of joint disease to illness (symptoms, disability and joint failure). It is possible that the threshold will vary according to type of joint disease. Both the kidney and liver have a large “functional reserve”.

Disease vs illness.
Plain radiography or magnetic resonance imaging (MRI): Which is better in assessing outcome in clinical trials of disease-modifying osteoarthritis drugs? Summary of a debate held at the World Congress of Osteoarthritis 2014

Seminars in Arthritis and Rheumatism 45 (2015) 251–256

Felix Eckstein, MD\textsuperscript{a,b,*}, Marie-Pierre Hellio Le Graverand, MD, PhD\textsuperscript{c}

ABSTRACT

Osteoarthritis (OA) is the most common disease of synovial joints and currently lacks treatment options that modify structural pathology. Imaging is ideally suited for directly evaluating efficacy of disease-modifying OA drugs (DMOADs) in clinical trials, with plain radiography and MRI being most often applied. The current article is based on a debate held on April 26, 2014, at the World Congress of Osteoarthritis: The authors were invited to contrast strengths and limitations of both methods, highlighting scientific evidence on reliability, construct-validity, and correlations with clinical outcome, and comparing their sensitivity to change in knee OA and sensitivity to DMOAD treatment. The authors concluded that MRI provides more comprehensive information on articular tissues pathology, and that implementation of radiography in clinical trials remains a challenge. However, neither technique has thus far been demonstrated to be strongly superior over the other; for the time being it therefore appears advisable to use both in parallel in clinical trials, to provide more evidence on their relative performance. Radiographic JSW strongly depends on adequate positioning; it is not specific to cartilage loss but also to the meniscus. MRI provides somewhat superior sensitivity to change compared with the commonly used non-fluoroscopic radiographic acquisition protocols, and has recently provided non-location-dependent measures of cartilage thickness loss and gain, which are potentially more sensitive in detecting DMOAD effects than radiographic JSW or region-specific MRI. Non-location-dependent measures of cartilage thickness change should thus be explored further in context of anabolic and anti-catabolic DMOADs.
MRI can detect OA with an overall high specificity and moderate sensitivity when compared with various reference standards.
MRI can detect OA with an overall high specificity and moderate sensitivity when compared with various reference standards.
The MRI approach proved to be a superior analysis tool for detecting changes in cartilage morphology over a 1-year period. Radiographically defined JSN was found to be the least responsive measurement method of knee OA disease progression.
Evidence suggests that semiquantitative (SQ) assessment of OA by MRI is valid, reliable and responsive, which helps investigators to understand the natural history of this complex disease and to evaluate potential new drugs in OA clinical trials.
What is the predictive value of MRI for the occurrence of knee replacement surgery in knee osteoarthritis?


Box 1  Economic aspects of osteoporosis and osteoarthritis statements on the predictive value of MRI for hard outcomes in knee osteoarthritis

Statement 1: Medial compartment cartilage volume/thickness loss may be a valid structural endpoint in RCT in knee osteoarthritis involving patients with late-stage osteoarthritis.
Statement 2: Other MRI outcomes including assessment of cartilage defects, bone marrow lesions, meniscal lesions and synovitis may also predict knee replacement, and may potentially serve as structural endpoints in clinical trials.
Statement 3: Integration of the information contained in MRI could eventually lead to a predictive tool for knee replacement.

MRI may prove to be a good alternative to radiography in definitions of knee replacement.
Prognostic factors for progression of clinical osteoarthritis of the knee: a systematic review of observational studies

Alex N. Bastick¹*, Jos Runhaar¹, Janneke N. Belo² and Sita M.A. Bierma-Zeinstra¹

The best evidence synthesis showed strong evidence that age, ethnicity, body mass index, co-morbidity count, magnetic resonance imaging (MRI) - detected infrapatellar synovitis, joint effusion and baseline OA severity (both radiographic and clinical) are associated with clinical knee OA progression.
MRI may become the imaging modality of choice in the future. MRI measures currently investigated include quantitative cartilage morphometry, bone marrow lesions and other joint structure changes on semi-quantitative analysis, bone shape/attrition and subchondral bone area.

**Medicinal products intended to slow or prevent structural damage**

- Watch out for ongoing initiatives to qualify biochemical markers and especially MRI as an imaging biomarker offering surrogacy over shorter periods and in smaller trials than with JSN.
The sources of pain in osteoarthritis: a pathophysiological review

*Reumatismo, 2014; 66 (1): 57-71*

F. Salaffi¹, A. Ciapetti¹, M. Carotti²
Glucosamine hydrochloride or sulfate

### Cartilage

- **Anti-inflammatory**
  - $\downarrow$ PLA$_2$
  - $\downarrow$ iNOS, COX-2
  - $\downarrow$ pro-inflammatory cytokines and chemokines
  - $\downarrow$ NF-$\kappa$B
  - $\uparrow$ GRP78
- **Anti-catabolic and anabolic**
  - $\downarrow$ MMPs
  - $\downarrow$ ADAMTS-5
  - $\uparrow$ GAG and HA production

### Subchondral bone

- **Anti-resorptive**
  - $\downarrow$ RANKL
  - $\uparrow$ OPG

### Synovial membrane

- **Anti-inflammatory**
  - $\downarrow$ TNFa and IL-1$\beta$
  - $\downarrow$ NO and PGE$_2$
  - $\uparrow$ IL-10
- **Anti-catabolic**
  - $\uparrow$ HAS, HA and GAG production
  - $\downarrow$ MAPK signaling pathway
- **Pro and anti-angiogenic**
The inflamed SM is the source of pain in the OA joint. There are changes in nociception, sensitization by inflammatory mediators, and production of specific neuropeptides.
Fluid sensitive sequences are capable of delineating intraarticular joint fluid. However, a distinction between true joint effusion and synovial thickening is not possible as both are visualized as hyperintense signal within the joint cavity. For this reason the term effusion-synovitis has been introduced (T2 fat sat).
Synovitis in knee osteoarthritis: a precursor of disease?

Effusion-synovitis strongly predicted the development of radiographic knee OA (ROA).

Infrapatellar fat pad (IPFP) signal intensity alteration at baseline was associated with knee structural abnormalities and clinical symptoms cross-sectionally and longitudinally in older adults, suggesting that it may serve as an important imaging biomarker in knee OA.
Current view of the infrapatellar fat pad (IFP) and its interaction with other joint tissues

The IFP (Hoffa) is a source of several soluble factors. Moreover, it is composed of adipocytes and stromal vascular cells, such as macrophages, T cells, and mesenchymal stem cells (MSCs). Cellular interactions have been described within the IFP, such as between adipocytes and macrophages or T cells but also between IFP and other joint tissues.
Magnetic resonance imaging of Hoffa's fat pad and relevance for osteoarthritis research: a narrative review

Osteoarthritis and Cartilage 24 (2016) 383–397

F.W. Roemer † ‡ *, M. Jarraya † §, D.T. Felson ||, D. Hayashi † ¶, M.D. Crema † #, D. Loeuille † † †, A. Guermazi †

Anatomy of Hoffa's fat pad

Sagittal T1
Hoffa-synovitis: intermediate-weighted fat suppressed image shows infrapatellar areas of hyperintensity within Hoffa’s fat pad (grade 2).

Hoffa-synovitis: Another knee exhibits marked signal alterations within Hoffa’s fat pad representing grade 3 Hoffa-synovitis (arrows)
Signal changes in Hoffa's fat pad are commonly used as a surrogate for synovitis on non contrast-enhanced MRI.

Hoffa-synovitis

Grade 1

Grade 2

Grade 3
Of the 3 locations for synovitis, changes in the infrapatellar fat pad were most strongly related to pain change.

Change in synovitis was correlated with change in knee pain.

Treatment of knee osteoarthritis (OA) needs to consider treatment of synovitis.
Imaging of cartilage and bone: promises and pitfalls in clinical trials of osteoarthritis

Osteoarthritis and Cartilage 22 (2014) 1516–1532

F. Eckstein † ‡ *, A. Guermazi § ‖, G. Gold ¶, J. Duryea #, M.-P. Hellio Le Graverand † †, W. Wirth † ‡, C.G. Miller ‡ ‡

Magnetic resonance imaging (MRI) provide powerful tools for scoring and measuring morphological and compositional aspects of most articular tissues, capturing longitudinal change with reasonable to excellent sensitivity.
Effusion-synovitis volume

Salaffi F et al. in press 2016
Degree of synovitis on MRI by comprehensive whole knee semi-quantitative scoring method correlates with histologic and macroscopic features of synovial tissue inflammation in knee osteoarthritis

B.J.E. de Lange-Brokaar ‡*, A. Ioan-Facsinay ‡, E. Yusuf ‡, A.W. Visser ‡, H.M. Kroon ¶, S.N. Andersen ‡, L. Herb-van Toorn ‡, G.J.V.M. van Osch ‡, A.-M. Zuurmond §, V. Stojanovic-Susulic ||, J.L. Bloem ¶, R.G.H.H. Nelissen #, T.W.J. Huizinga ‡, M. Kloppenburg ‡‡‡

Osteoarthritis and Cartilage 22 (2014) 1606–1613

Synovitis severity on contrast enhanced (CE-MRI) assessed by a new whole knee scoring is a valid, non-invasive method to determine synovitis as it is significantly correlated with both macroscopic and microscopic features of synovitis in knee OA patients.
Glucosamine hydrochloride or sulfate

**Cartilage**

<table>
<thead>
<tr>
<th>Function</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-inflammatory</td>
<td>↓ PLA₂, ↓ iNOS, COX-2, ↓ pro-inflammatory cytokines and chemokines, ↓ NF-κB, ↑ GRP78</td>
</tr>
<tr>
<td>Anti-catabolic and anabolic</td>
<td>↓ MMPs, ↓ ADAMTS-5, ↑ GAG and HA production</td>
</tr>
</tbody>
</table>

**Subchondral bone**

<table>
<thead>
<tr>
<th>Function</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-resorptive</td>
<td>↓ RANKL, ↑ OPG</td>
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</table>

**Synovial membrane**

<table>
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<tr>
<th>Function</th>
<th>Effects</th>
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<tbody>
<tr>
<td>Anti-inflammatory</td>
<td>↓ TNFα and IL-1β, ↓ NO and PGE₂, ↑ IL-10</td>
</tr>
<tr>
<td>Anti-catabolic</td>
<td>↑ HAS, HA and GAG production, ↓ MAPK signaling pathway</td>
</tr>
<tr>
<td>Pro and anti-angiogenic</td>
<td></td>
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</tbody>
</table>
A reduction in central medial femoro-tibial compartment cartilage thickness was strongly associated with radiographic progression (OR 4.0 P < 0.0001)
Coronal proton density-weighted fat-suppressed image shows excellent differentiation of articular cartilage, subchondral bone, and intraarticular joint fluid.

Sagittal proton density-weighted suppressed 3D fast low-angle shot.
Sagittal intermediate-weighted fat suppressed image) shows focal fullthickness cartilage defect (arrows) on posterior aspect of lateral tibial plateau. Defect is well delineated because of high contrast between intraarticular fluid and cartilage surface.
Sagittal T2 fat sat 3D image depicts full-thickness chondral defect (arrows). Accompanying osteochondral depression at the lateral femoral condyle.

Standard sagittal T2 fat sat 2D Image shows defect (arrows) in similar fashion.
Evolution of cartilage damage over time

Baseline fat-suppressed intermediate-weighted MRI shows an intact articular cartilage surface

12 months later areas of partial and full thickness cartilage damage

Another 12 months later there is definite increase in area extent of lesion
3D reconstruction and visualization of knee cartilage plates from a sagittal MR imaging data set: medial tibial cartilage marked blue, medial femoral cartilage marked yellow, lateral tibial cartilage marked green, lateral femoral cartilage marked red, femoral trochlear cartilage marked turquoise, and patellar cartilage marked magenta.
In summary, this study argues for a structural beneficial effect of treatment with Glu/CS in subsets of knee OA patients, as assessed by qMRI. This study is the first to describe, using qMRI, the impact of medial meniscal extrusion on the Glu/CS treatment response.

Glu/CS has a positive effect on cartilage volume loss assessed by quantitative MRI in symptomatic knee OA patients.
Treatment with combined glucosamine (Glu) and chondroitin sulfate (CS) significantly reduced the cartilage volume loss in the global knee, associated with the lateral compartment. Multivariate analysis further demonstrated that the extent of the treatment’s positive effect was related to exposure time to treatment, the protective effect at 6 years being significant in participants exposed to two or more years of treatment.
In analgesic/NSAIDs groups and – analgesic/NSAIDs groups, participants who took Glu/CS had reduced loss of cartilage volume over 24 months in subregions when assessed with qMRI, arguing for a disease-modifying effect of Glu/CS which could not be identified by X-rays.

These data are consistent with the hypothesis that individuals with milder structural changes would benefit more from structure-modifying agents, such as Glu/CS, than those with a more advanced disease.
### Glucosamine hydrochloride or sulfate

#### Cartilage
- Anti-inflammatory
  - ↓ PLA₂
  - ↓ iNOS, COX-2
  - ↓ pro-inflammatory cytokines and chemokines
  - ↓ NF-κB
  - ↑ GRP78
- Anti-catabolic and anabolic
  - ↓ MMPs
  - ↓ ADAMTS-5
  - ↑ GAG and HA production

#### Subchondral bone
- Anti-resorptive
  - ↓ RANKL
  - ↑ OPG

#### Synovial membrane
- Anti-inflammatory
  - ↓ TNFa and IL-1β
  - ↓ NO and PGE₂
    - ↑ IL-10
- Anti-catabolic
- ↑ HAS, HA and GAG production
  - ↓ MAPK signaling pathway
- Pro and anti-angiogenic
Bone marrow lesion (BML) size may be an important imaging biomarker for osteoarthritis-related clinical trials and reducing BML size may be an important therapeutic goal.

Large baseline BMLs are associated with greater baseline knee pain, the presence of JSN at baseline, and disease progression. Additionally, BML regression is associated with decreased knee pain but not a reduced risk of concurrent JSN progression.

Driban et al. Arthritis Research & Therapy 2013, 15:R112
Bone marrow edema and bone marrow lesions depicted on the medial femur on a T2-weighted fat suppressed MRI (A) and medial tibial plateau on an intermediate-weighted fat suppressed MRI (B).
a: Sagittal intermediate-weighted (IW) fat-suppressed (fs) image shows a large (grade 3) subchondral bone marrow edema-like lesion at the lateral femoral trochlea (white arrows). Within this lesion, there is a small subchondral cyst (grade 1) directly adjacent to the subchondral plate (black arrowhead). b: Corresponding sagittal Dual Echo Steady-State (DESS) image only shows the small cyst (white arrow).
SEGMENTAZIONE SEMIAUTOMATICA CON OSIRIX

Sagittal GRE - T2
Advances in Imaging of Osteoarthritis and Cartilage

Whole-organ semiquantitative MR imaging-based knee assessment is a reliable instrument to evaluate all tissues involved in the osteoarthritic disease process and may be applied in cross-sectional and longitudinal studies.

Quantitative 3D cartilage morphometry is a validated and reliable tool to assess several cartilage parameters cross-sectionally and in a longitudinal fashion and is complementary to other evaluation techniques.

Compositional MR imaging might play an important role in the assessment of early and potentially reversible cartilage damage, and several techniques are available and applicable in a clinical setting.

MR Imaging of Biochemical Properties of Articular Cartilage
The role of quantitative imaging techniques in OA is emerging because they detect cartilage disease at earlier stages than radiography and conventional MRI, and provide outcome measures that can be used as imaging biomarkers in clinical research.

Quantitative imaging techniques for cartilage composition are likely to play a pivotal role in future research and development of disease-modifying therapy for arthritis.
Mapping software allows visualization of the spatial distribution; notice the increased T2 relaxation times in Fig. B. The T2 relaxation time is overlaid on the images using a color map, with the scale in milliseconds.
Compositional MR imaging.

A) Sagittal proton density–weighted high-spatial-resolution 3-T MR image of medial compartment of a knee with tibiofemoral OA shows peripheral (black arrows) and central (arrowhead) osteophytes.

B) (B) Delayed gadolinium-enhanced MR imaging of cartilage (dGEMRIC) T1 map corresponding to a shows multiple areas with low T1 values, corresponding to low GAG content in superficial layers of femoral cartilage and in posterior part of tibial cartilage (dark blue).

C) Sagittal T2 map corresponding to a reveals several areas of increased T2 values in femoral medial condyle.
Sodium maps of articular cartilage in a healthy volunteer (A) and a patient with OA (B) overlaid onto proton images. The increased sodium signal correlates with higher glycosaminoglycan (GAG) concentration. As cartilage degenerates and GAG concentration decreases, sodium signal declines.
Stages of OA incorporating the new taxonomy. Three stages can be imagined: a no disease/no illness stage, a subclinical stage (with disease manifestations only) and a clinical stage (with illness manifestations).
The Future of Osteoarthritis Therapeutics: Targeted Pharmacological Therapy

A. Mobasherari

Curr Rheumatol Rep (2013) 15:364

*Schematic diagram summarizing current concepts in pharmacological treatment of OA*
The hallmarks of osteoarthritis and the potential to develop personalised disease-modifying pharmacological therapeutics

D.P. Tonge ‡, M.J. Pearson †, S.W. Jones †

**Synovium**
- Inhibition of synovial inflammation
  - Arachidonic acid pathway inhibitors (e.g. Licoelone)
  - p38 pathway inhibitors (e.g. MK2)
  - Inducible nitric oxide synthase (NOS) inhibitors

**Skeletal Muscle**
- [combination with adjuvant exercise program]
  - Inhibition of myofibrillar degradation
  - Selective androgen receptor modulators (SARMs)
  - B2-adrenergic agonists

**Cartilage**
- Inhibition of catabolic proteases
  - Specific MMP inhibitors (e.g. MMP13)
  - Aggrecanase inhibitors (ADAMTS4, ADAMTS5)

- Anabolic promotion
  - Growth Factors (e.g. FGF2, FGF18)
  - BMP7

- Novel combinations of known targets
  - e.g. Protease inhibitor + anabolic

**Subchondral Bone**
- Inhibition of osteoclast activity
  - Protease inhibitors (e.g. CatK)
  - Apoptosis inducers (e.g. Strontium Ranelate)

- Bone vasculature targets
  - Angiogenic modulators
  - Candidate drug repurposing (from CV Therapeutic area)

**Adipose Tissue**
- [combination with adjuvant weight-loss program]
  - Modulation of adipokine signalling
  - Leptin pathway inhibitors (e.g. Leptin mAb)
  - Resistin pathway inhibitors
  - APN pathway activators (e.g. recombinant/mimetic APN)

Representation of the multiple biological effect areas within the OA joint and key pathways to exploit for the development of pharmacological DMOADs.