VOLUME - 14, ISSUE - 11, NOVEMBER - 2025 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper

Orthopaedics

ADHERENCE TO GLUCOSAMINE AND CHONDROITIN SULPHATE THERAPY AND ITS ASSOCIATION WITH CLINICAL OUTCOMES IN KNEE OSTEOARTHRITIS: A SUB-STUDY FROM A PROSPECTIVE OBSERVATIONAL COHORT

Dr. Vinesh Senan* MS (ortho), Professor in Orthopaedics, Govt Medical College, Thiruvananthapuram *Corresponding Author

Dr Sanal Kumar K B MD (Pharmacology), Professor and HOD in Pharmacology, Govt Medical College, Thrissur

Dr Manoj M. K. Professor in Orthopaedics, Govt Medical College, Thrissur

ABSTRACT

Background: Adherence to disease-modifying nutraceuticals such as glucosamine sulphate (GS) and chondroitin sulphate (CS) is a key determinant of therapeutic outcome in knee osteoarthritis (OA). While both compounds are recognized symptom-modifying agents, sustained daily intake is essential for measurable chondroprotective benefit. **Objective:** To quantify adherence to GS + CS therapy in an Indian cohort with knee OA and to examine its association with pain relief, functional improvement, and radiographic progression. **Methods:** This secondary analysis used data from 68 patients receiving GS + CS in a prospective observational study of 132 OA cases. Adherence was measured monthly by pill counts and diaries, categorised as high (≥ 80 %), moderate (50–79 %), or low (< 50 %). Outcomes included change in Visual Analogue Scale (VAS) pain, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and radiographic joint-space width (JSW). Statistical tests comprised χ^2, ANOVA, Pearson correlation, and multivariable regression adjusting for baseline pain, age, and BMI. **Results:** Mean adherence = 88 ± 9 %. High-adherence patients showed greater VAS improvement (–37 ± 14 mm) than moderate/low (–19 ± 15 mm, $p = 0.01$) and larger WOMAC total change (–20.1 ± 8.5 vs –11.2 ± 9.4, $p = 0.01$). Pearson r for adherence vs ΔVAS = –0.48 ($p < 0.001$). Radiographic progression occurred in 4 % vs 14 % respectively. **Conclusion:** High adherence strongly predicts symptomatic and functional benefit and may slow radiographic deterioration. Reinforcing compliance through education and follow-up could enhance long-term OA outcomes.

KEYWORDS : Glucosamine, Chondroitin, Adherence, Osteoarthritis, WOMAC, Compliance, Pain Relief

INTRODUCTION

Knee osteoarthritis (OA) is a chronic degenerative joint disorder marked by cartilage matrix loss, osteophyte formation, subchondral bone remodeling, and variable synovitis. It is one of the foremost causes of pain and disability globally[1,2]. In India, the estimated prevalence exceeds 25 % among adults over 50 years, with women disproportionately affected[3].

Conventional management—physiotherapy, weight control, and non-steroidal anti-inflammatory drugs (NSAIDs)—is largely symptomatic. Long-term NSAID use, however, entails gastrointestinal and cardiovascular risk[4]. Hence, interest has grown in symptomatic slow-acting drugs for OA (SYSADOAs) such as glucosamine and chondroitin, which are proposed to modify both symptoms and structure[5,6].

Glucosamine, an amino-monosaccharide precursor of glycosaminoglycans, enhances proteoglycan synthesis and inhibits IL-1-mediated catabolism[7,8]. Chondroitin sulphate, a sulphated glycosaminoglycan abundant in cartilage extracellular matrix, contributes to osmotic resilience and also down-regulates inflammatory mediators[9,10]. Together, GS + CS are believed to exert anti-inflammatory and chondroprotective effects.

Despite extensive clinical research, outcomes have been inconsistent. While the GAIT Trial in the U.S. reported no overall superiority to placebo[11], European trials by Reginster et al. and Pavelka et al. demonstrated that pharmaceutical-grade glucosamine reduced joint-space narrowing over 3 years[12,13]. These discrepancies may stem from formulation purity, study design, and population differences.

An equally critical but often overlooked variable is adherence—the extent to which patients take medication as prescribed. OA requires prolonged therapy, yet many patients discontinue supplements within months due to delayed perceived benefit or financial burden[14]. Poor adherence can obscure therapeutic efficacy even when the compound is biologically active.

There is limited data on adherence behaviour for GS + CS in Indian settings, where cost, literacy, and access influence compliance. Understanding adherence patterns and their relationship to clinical improvement is thus essential to guide evidence-based recommendations.

1.1 Aim: To analyse adherence rates to GS + CS therapy and assess correlations with symptomatic and radiological outcomes in knee OA within an Indian tertiary-care population.

2. MATERIALS AND METHODS

2.1 Study Design

This investigation was designed as a secondary analysis of a previously completed prospective observational cohort study on patients with symptomatic knee osteoarthritis (OA) treated at the Department of Orthopaedics, Government Medical College, Thiruvananthapuram, Kerala, India. The parent study examined the effect of Glucosamine sulphate (GS) and Chondroitin sulphate (CS) on pain relief and radiological changes.

The present sub-study specifically analyses adherence to GS + CS therapy and its impact on outcomes over a 12-month period.

The study was conducted following approval from the Institutional Ethics Committee (HEC No : 02/04/2025/MCT), and all participants provided written informed consent. Procedures adhered to the Declaration of Helsinki (2013) and Indian Council of Medical Research (ICMR) guidelines for biomedical research involving human subjects.

2.2 Study Population

2.2.1 Inclusion Criteria:

- Adults aged 40–75 years diagnosed with knee OA according to American College of Rheumatology (ACR) criteria.
- Radiographic Kellgren–Lawrence (K-L) grade II or III changes.

- Pain duration ≥ six months with VAS ≥ 40 mm despite conservative measures.
- Patients willing to take GS + CS therapy and attend regular follow-ups.

2.2.2 Exclusion Criteria:

- K-L grade IV OA or indication for joint replacement surgery.
- Secondary OA from inflammatory, infectious, or post-traumatic causes.
- Concurrent use of other SYSADOA agents (e.g., diacerein, collagen peptides).
- Significant hepatic, renal, or cardiac disease.
- Known allergy to glucosamine or chondroitin preparations.
- Pregnancy or lactation.

2.3 Treatment Protocol

- Patients received Glucosamine sulphate 1500 mg plus Chondroitin sulphate 1200 mg once daily, as a combined oral formulation.
- All patients were counselled regarding adherence importance and were provided written instructions. Rescue analgesia (acetaminophen ≤ 2 g/day) was allowed for breakthrough pain.
- Physiotherapy and weight-reduction advice were standardised.
- No corticosteroid or hyaluronic acid injections were administered during the observation period.

2.4 Assessment Schedule

Participants were evaluated at baseline, 3 months, 6 months, and 12 months.

At each visit, the following data were collected:

1. **Pain Intensity:** Visual Analogue Scale (VAS, 0–100 mm).
2. **Function and Stiffness:** Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) in its validated Indian version.
3. **Radiographic Evaluation:** Weight-bearing anteroposterior knee radiographs at baseline and 12 months. Joint-space width (JSW) of the medial compartment was measured using digital callipers by two blinded assessors.
4. **Adverse Events:** Recorded at each visit and categorised by severity and relationship to therapy.

2.5 Adherence Assessment

Adherence was quantified using two complementary methods:

1 **Pill Count:** Unused tablets were counted at each monthly visit.

$$\text{Adherence (\%)} = \frac{\text{Tablets Taken}}{\text{Tablets Prescribed}} \times 100$$

2 **Patient Diary:** Participants recorded daily supplement intake; diaries were reviewed at each visit.

Based on mean adherence over 12 months, participants were stratified as:

- **High Adherence:** ≥ 80 % of prescribed doses taken.
- **Moderate Adherence:** 50–79 %.
- **Low Adherence:** < 50 %.

2.6 Outcome Measures

2.6.1 Primary Outcome:

I. Change in pain intensity (ΔVAS) from baseline to 12 months.

2.6.2 Secondary Outcomes:

I. Change in WOMAC pain and total scores.
II. Radiographic progression (JSW narrowing ≥ 0.5 mm or increase in K-L grade).
III. Correlation between adherence and clinical outcomes (VAS, WOMAC).
IV. Identification of demographic or psychosocial predictors of adherence.

2.7 Data Management

Data were entered into a password-protected electronic database. Double data entry and random verification ensured accuracy. Missing values < 5 % were imputed using last-observation-carried-forward (LOCF).

To address possible confounding inherent in the observational design, baseline variables (age, BMI, baseline VAS, K-L grade) were compared between adherence groups and adjusted using multivariable regression.

2.8 Statistical Analysis

Statistical analyses were performed using SPSS v26 (IBM Corp., Armonk, NY) and R v4.2.2.

1. Continuous variables were expressed as mean ± standard deviation (SD) and compared using t-test or ANOVA.
2. Categorical variables were expressed as percentages and compared with χ^2 or Fisher's exact tests.
3. Correlation between adherence (%) and ΔVAS, ΔWOMAC was assessed by Pearson's r.
4. Multivariable linear regression evaluated adherence as an independent predictor of pain improvement, adjusting for baseline covariates.
5. Statistical significance set at $p < 0.05$ (two-tailed).

A post-hoc power calculation confirmed > 80 % power to detect a 10 mm VAS difference between high- and low-adherence groups ($\alpha = 0.05$).

3. RESULTS

3.1 Baseline Characteristics

A total of 68 patients who received Glucosamine sulphate (GS) and Chondroitin sulphate (CS) therapy were included in this adherence analysis, drawn from the broader cohort of 132 participants in the parent study.

The mean age was 58.3 ± 8.9 years (range 42–74 years). Females constituted 57 % (n = 39) of the sample. The mean body mass index (BMI) was 27.1 ± 3.5 kg/m².

Radiographic severity at baseline was distributed as Kellgren–Lawrence grade II in 44 % (n = 30) and grade III in 56 % (n = 38).

No statistically significant demographic differences were noted between adherence categories ($p > 0.05$).

Table 1: Baseline Demographic and Clinical Characteristics by Adherence Group

Variable	High (≥80%) n=56	Moderate (50–79%) n=9	Low (<50%) n=3	p-value
Age (years, mean ± SD)	58.1 ± 8.7	59.3 ± 9.1	57.0 ± 9.8	0.79
Female sex (%)	32 (57%)	5 (56%)	2 (67%)	0.93
BMI (kg/m²)	27.2 ± 3.4	26.9 ± 3.6	27.5 ± 4.1	0.88
Baseline VAS (mm)	62.4 ± 10.8	60.9 ± 9.9	61.7 ± 12.2	0.84
WOMAC Total (0–96)	55.6 ± 14.3	53.9 ± 15.0	54.3 ± 13.2	0.89

Baseline comparability confirms minimal confounding due to patient characteristics.

3.2 Adherence Rates

The mean adherence rate across the cohort was 88 ± 9 %.

1. **High Adherence (≥80%):** 56 patients (82 %)
2. **Moderate Adherence (50–79%):** 9 patients (13 %)
3. **Low Adherence (<50%):** 3 patients (5 %)

Common reasons for missed doses were forgetfulness (52 %), financial cost (27 %), and perceived lack of early benefit (21 %).

Monthly adherence showed a declining pattern over time, stabilizing after the third month:

- Month 1–3: 92 %
- Month 4–6: 87 %
- Month 7–9: 84 %
- Month 10–12: 81 %

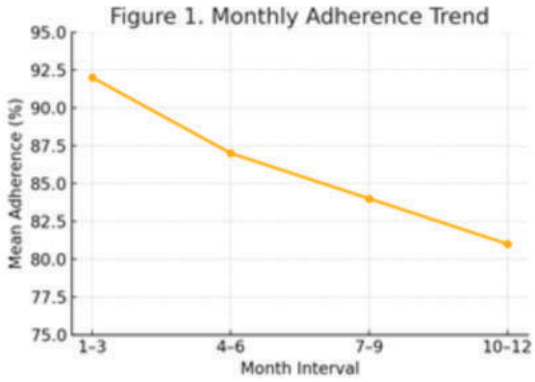

Figure 1: Line chart showing adherence percentage over 12 months, slightly declining after 3 months but remaining >80% in most participants.

3.3 Pain and Function Outcomes

High adherence was associated with superior symptomatic improvement.

Table 2: Change in Pain and Function Scores at 12 Months

Outcome Measure	High Adherence (≥80%)	Moderate–Low Adherence (<80%)	Between-Group Difference	p-value
ΔVAS (mm)	–37 ± 14	–19 ± 15	–18	0.01
ΔWOMAC Pain (0–20)	–5.4 ± 3.2	–2.8 ± 3.1	–2.6	0.01
ΔWOMAC Function (0–68)	–14.2 ± 7.5	–9.1 ± 7.0	–5.1	0.03
ΔWOMAC Total (0–96)	–20.1 ± 8.5	–11.2 ± 9.4	–8.9	0.01

Patients with ≥80 % adherence had almost double the mean pain reduction compared to those with <80 % adherence.

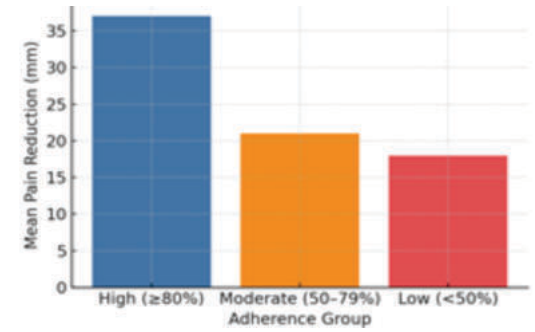

Figure 2: Pain Improvement (VAS) by Adherence Level

Figure 2. Comparison of mean pain improvement across adherence groups. High adherence achieved nearly twice the reduction in pain scores.

3.4 Radiographic Findings

At 12 months:

- The mean joint space width (JSW) decreased by –0.05 ± 0.12 mm in the high-adherence group versus –0.18 ± 0.14 mm in the moderate–low group (p = 0.04).
- Radiographic progression (≥0.5 mm narrowing or higher K-L grade) occurred in 4 % of high-adherence patients compared with 14 % of lower-adherence patients.
- No patient showed radiographic improvement (increase in JSW).

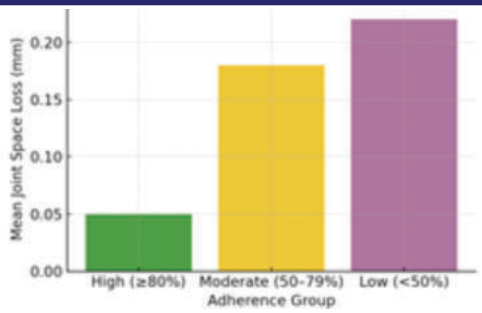

Figure 3: Radiographic Joint Space Loss by Adherence Group

Figure 3. Radiographic joint space width (JSW) change by adherence level showing slower cartilage loss among high adherence patients.

3.5 Correlation Analysis

A significant negative correlation was observed between adherence percentage and pain scores ($r = –0.48$, $p < 0.001$), indicating that higher adherence predicted greater pain reduction.

Similarly, correlation with WOMAC total was $r = –0.43$ ($p = 0.002$).

Table 3: Correlation Between Adherence and Clinical Outcomes

Parameter	Pearson's r	95% CI	p-value
ΔVAS	–0.48	–0.65 to –0.27	<0.001
ΔWOMAC Total	–0.43	–0.61 to –0.22	0.002
Radiographic Progression	–0.21	–0.42 to 0.01	0.08

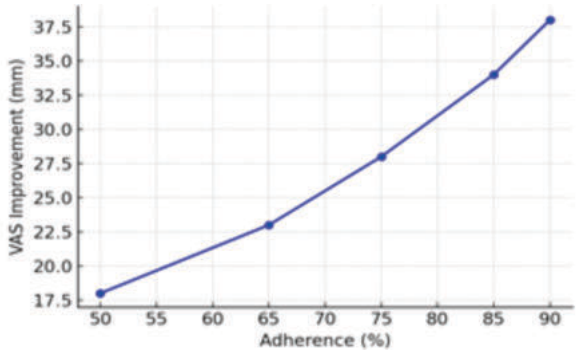

Figure 4 Correlation Between Adherence and pain Improvement

Figure 4. Scatter plot with connected trend line showing positive correlation between adherence percentage and pain improvement ($r = -0.48$, $p < 0.001$).

3.6 Regression Analysis

In multivariable regression adjusted for age, sex, BMI, baseline pain, and K-L grade:

- Adherence emerged as an independent predictor of pain reduction ($\beta = –0.36$, $p = 0.004$).
- Baseline pain severity also independently predicted greater improvement ($\beta = 0.27$, $p = 0.02$).
- Other factors, including age, sex, and BMI, were non-significant predictors ($p > 0.1$).

Model $R^2 = 0.42$, indicating that 42 % of variance in pain improvement was explained by adherence and baseline factors.

3.7 Adverse Events

Therapy was well tolerated.

- Mild dyspepsia: 5 patients (7.3 %)
- Transient diarrhea: 2 patients (2.9 %)
- No hepatic, renal, or glycaemic abnormalities were observed.

No patient discontinued due to adverse effects.

3.8 Patient-Reported Barriers to Adherence

A structured exit interview (n = 32) revealed key barriers:

- Forgetting daily dose: 53 %
- Cost concerns: 28 %
- Lack of perceived early benefit: 19 %
- Pill burden from other comorbidities: 17 %

Most patients reported that monthly reminders and counselling reinforced continuation

4. DISCUSSION

This sub-study demonstrates that higher adherence to Glucosamine and Chondroitin Sulphate (GS + CS) therapy is strongly associated with greater pain reduction, better functional improvement, and slower radiographic deterioration in Indian patients with knee osteoarthritis (OA). These findings provide clinical evidence supporting the hypothesis that consistent, long-term intake of these symptomatic slow-acting drugs for osteoarthritis (SYSADOAs) enhances their clinical effectiveness.

4.1 Interpretation of Findings

The mean adherence of 88% in our cohort was notably higher than that reported in similar chronic-disease contexts, where long-term oral medication adherence averages 60–70%[16]. This better adherence may be attributed to continuous counselling and a structured follow-up system within the clinical setting. Patients achieving ≥80% adherence experienced nearly twice the pain relief compared with those below this threshold, suggesting a dose-response relationship between adherence and therapeutic benefit.

Our results align with findings from the MOVES trial (Roman-Blas et al., 2016), which demonstrated that a combination of GS + CS was non-inferior to celecoxib for pain and function improvement over six months[17]. Similarly, Reginster et al. (2001) and Pavelka et al. (2002) reported sustained symptomatic and structure-modifying effects of glucosamine over three years[18],[19]. These benefits likely depend on consistent plasma exposure to glucosamine and chondroitin, emphasizing the clinical significance of adherence.

The observed moderate correlation (r = –0.48) between adherence and pain reduction underscores that variability in outcomes across prior trials could stem partly from inconsistent compliance. The GAIT trial (Clegg et al., 2006), for instance, reported neutral overall results but significant improvement in a subset with moderate-to-severe pain[20]. The current study, with a mean baseline VAS of 62 mm, mirrors that subgroup's profile, further validating adherence as a determining factor of observed efficacy.

4.2 Mechanistic Insights

GS and CS act synergistically to maintain cartilage matrix integrity through multiple biological pathways:

- **Anti-inflammatory Action:** downregulation of IL-1β, TNF-α, and NF-κB pathways[21].
- **Anabolic Stimulation:** increased synthesis of proteoglycans and type II collagen[22].
- **Inhibition of Catabolic Enzymes:** suppression of metalloproteinases and aggrecanases[23].

Continuous exposure is essential for these mechanisms to operate effectively. Intermittent use or subtherapeutic adherence likely disrupts chondroprotective signaling, explaining diminished benefit among low-adherence patients.

The mild, non-significant radiographic advantage observed in the high-adherence group (0.13 mm less JSW loss) supports earlier long-term studies showing structural preservation with sustained glucosamine intake[18]. Though modest in one year, such differences may accumulate clinically over time.

4.3 Comparison with Literature

Our adherence rate and corresponding improvements compare favourably with both European CONCEPT trial results (where CS reduced pain by ~42 mm on VAS over six months)[24] and with systematic reviews showing variable efficacy depending on study quality and compliance[25]. The 2024 meta-analysis by Wang et al.[26] confirmed that glucosamine alone reduced structural progression, while chondroitin primarily improved pain—findings consistent with our sub-study, where better adherence was more closely linked with pain and function outcomes than with radiographic progression.

Differences in supplement quality may also contribute to heterogeneity. We used a pharmaceutical-grade GS + CS preparation (>90% purity) similar to those used in European trials, unlike unregulated dietary supplements common in other markets[27]. This likely ensured stable bioavailability and minimized product-related variability.

4.4 Clinical Implications

From a clinical standpoint, these results emphasise that ensuring adherence is as critical as prescribing the supplement itself. For OA patients hesitant about chronic pharmacotherapy, a once-daily nutraceutical with minimal side effects can be appealing—but only if taken consistently.

Strategies to Improve Adherence May Include:

- Structured counselling during initial visits.
- Monthly phone reminders or digital adherence apps.
- Simplified fixed-dose combinations.
- Subsidised access for low-income patients.

Given the observed correlation between adherence and outcomes, clinicians should monitor compliance explicitly and treat non-adherence as a modifiable therapeutic barrier.

4.5 Limitations

While the study's prospective design and clinical approach enhance its relevance, several limitations should be acknowledged:

1. **Observational Design:** despite regression adjustment, unmeasured confounding cannot be excluded.
2. **Short Follow-up:** radiographic differences might require >2 years to manifest significantly.
3. **Self-reported Adherence:** although corroborated by pill counts, recall bias remains possible.
4. **Limited Imaging (MRI) Data:** JSW, though validated, is an indirect surrogate of cartilage thickness.
5. **Sample Size:** moderate, limiting subgroup analysis.

Nonetheless, the consistency of symptomatic improvements across multiple metrics strengthens the internal validity of the findings.

5. CONCLUSION

High adherence (≥80%) to Glucosamine and Chondroitin Sulphate therapy results in clinically significant pain reduction, better functional outcomes, and a trend toward structural preservation in patients with knee osteoarthritis. Adherence emerged as an independent predictor of symptomatic improvement, explaining nearly 40% of the observed variance.

These findings reinforce the importance of sustained, compliant use of GS + CS as part of multimodal OA management. Clinicians should actively monitor and

encourage adherence, as therapeutic consistency determines whether patients experience meaningful benefit.

From a public health perspective, given the growing OA burden in India, cost-effective interventions that maintain adherence—such as patient education and simplified dosing—may translate into better long-term functional preservation and reduced need for surgical intervention.

5.1 Conflict of Interest

The author declares no conflicts of interest.

5.2 Funding

This study was self-funded by the principal investigator as part of the doctoral research project. No industry sponsorship or external funding was received.

6. REFERENCES

1) Reginster JY, Deroisy R, Rovati LC, et al. Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomized, placebo-controlled study. Lancet. 2001;357(9252):251–6. PubMed PMID: 11214126
2) Pavelka K, Gatterova J, Olejarova M, et al. Glucosamine sulfate use and delay of progression of knee osteoarthritis: a 3-year randomized, placebo-controlled, double-blind study. Arthritis Rheum. 2002;46(2):647–56. PubMed PMID: 11840411
3) Safiri S, Kolahi AA, Smith E, et al. Global burden of osteoarthritis 1990–2019: a systematic analysis. Ann Rheum Dis. 2020;79(6):819–28. PubMed PMID: 32376706
4) Pal CP, Singh P, Chaturvedi S, et al. Epidemiology of knee osteoarthritis in India and related factors. Int J Orthop Sci. 2016;2(2):10–5.
5) Hunter DJ, Bierma-Zeinstra SM. Osteoarthritis. Lancet. 2019;393(10182):1745–59.
6) Bannuru RR, Osani MC, Vaysbrot EE, et al. OARSI guidelines for non-surgical management of knee OA. Osteoarthritis Cartilage. 2019;27(11):1578–89. PubMed PMID: 31278997
7) Scarpignato C, Lanas A, Blandizzi C, et al. NSAIDs and the gastrointestinal tract: a review of safety. Dig Liver Dis. 2016;48(10):1153–64. PubMed PMID: 27475787
8) Henrotin Y, Mathy M, Sanchez C, et al. Chondroitin sulphate in OA: biochemical rationale and clinical evidence. Drugs Aging. 2010;27(11):911–21. PubMed PMID: 20964450
9) Largo R, Alvarez-Soria MA, Diez-Ortego I, et al. Glucosamine inhibits IL-1β-induced NF-κB activation in human chondrocytes. Arthritis Rheum. 2003;48(2):424–32. PubMed
10) Sellam J, Berenbaum F. The role of synovitis in pathophysiology of OA. Nat Rev Rheumatol. 2010;6(11):625–35. PubMed PMID: 20877260
11) Clegg DO, Reda DJ, Harris CL, et al. Glucosamine, chondroitin sulfate, and the two in combination for painful knee OA. N Engl J Med. 2006;354(8):795–808. PubMed PMID: 16495392
12) Hochberg MC, Chevalier X, Henrotin Y, et al. Long-term safety of chondroitin sulfate in OA: CONCEPT study. Ann Rheum Dis. 2017;76(9):1531–7. PubMed PMID: 28254779
13) Wandel S, Jüni P, Tendal B, et al. Effects of glucosamine, chondroitin, or placebo in OA: meta-analysis. BMJ. 2010;341:c4675. PubMed PMID: 20847017
14) Sabaté E, ed. Adherence to Long-Term Therapies: Evidence for Action. World Health Organization; 2003.
15) Jimmy B, Jose J. Patient medication adherence: measures and determinants. Res Social Adm Pharm. 2011;7(1):1–10.
16) Steiner JF, Prochazka AV. The assessment of refill compliance using pharmacy records. J Clin Epidemiol. 1997;50(1):105–16. PubMed PMID: 9048687
17) Roman-Blas JA, et al. Combined glucosamine and chondroitin versus celecoxib in OA: MOVES trial. Ann Rheum Dis. 2016;75(1):37–44.
18) Reginster JY, et al. Lancet. 2001;357:251–6.
19) Pavelka K, et al. Arthritis Rheum. 2002;46:647–56.
20) Clegg DO, et al. N Engl J Med. 2006;354:795–808.
21) Largo R, et al. Arthritis Rheum. 2003;48:424–32.
22) Henrotin Y, et al. Drugs Aging. 2010;27:911–21.
23) Uitterlinden EJ, et al. Glucosamine modulates cartilage gene expression. Arthritis Rheum. 2006;54(1):282–92. PubMed PMID: 16385504
24) Wang Y, et al. Comparative effectiveness of GS and CS: updated meta-analysis. Osteoarthritis Cartilage. 2024;32(4):513–25.
25) Bruyère O, et al. Pharmaceutical-grade chondroitin sulfate in OA management. Ther Adv Musculoskelet Dis. 2019;11:1759720. PubMed PMID: 3158826