



Low dose NSAIDs and sysadoas in the management of knee osteoarthritis

Alberto Migliore¹ · Orazio De Lucia² · Alessandro de Sire^{3,4} · Andrea Šajbidor^{5,6} · Ladislav Šenolt^{7,8} ·
Sándor Szántó⁹ · Joan Calvet Fontova¹⁰ · Johannes Flechtenmacher¹¹ · Ali Mobasheri^{12,13,14} ·
Jordi Monfort Faure¹⁵ · Jean-Yves Reginster¹⁶ · Nicola Veronese^{17,18}

Received: 19 August 2025 / Revised: 13 September 2025 / Accepted: 19 September 2025
© The Author(s) 2025

Abstract

Introduction Osteoarthritis (OA) is a chronic, progressive joint disease characterized by the degradation of articular cartilage, subchondral bone remodeling, synovial inflammation, and osteophyte formation. Despite being a leading cause of disability in older people, effective long-term management of OA remains a significant challenge. Current treatment strategies primarily focus on symptom control, with both non-pharmacological and pharmacological interventions.

Materials and methods A systematic literature review followed by a structured Delphi survey was conducted, involving an international Technical Expert Panel (TEP) of OA specialists. The panel evaluated the efficacy, safety, and clinical utility of combining low dose diclofenac and chondroitin sulfate in OA management.

Results The analysis of expert consensus indicated that the combination of low dose diclofenac and chondroitin sulfate may be effective in reducing pain and improving joint function in patients with knee OA. Additionally, this combination could reduce the need for higher doses of NSAIDs, thereby minimizing systemic adverse effects.

Conclusion The combination of low dose diclofenac and chondroitin sulfate represents a promising therapeutic strategy for managing knee OA. Further studies are needed to confirm these findings and optimize therapeutic strategies to improve patient outcomes.

Keywords Osteoarthritis · Knee osteoarthritis · Diclofenac · Chondroitin sulfate · Low dose diclofenac · NSAIDs

Introduction

Osteoarthritis (OA) is a chronic, progressive, and multifactorial joint disease that represents one of the most prevalent musculoskeletal disorders worldwide [1, 2]. It is characterized by the degradation of articular cartilage, subchondral bone remodeling, synovial inflammation, and osteophyte formation, leading to pain, stiffness, and functional impairment. OA primarily affects weight-bearing joints, such as the knees and hips, but can also involve other joints, significantly impacting mobility and quality of life [3, 4]. With the global increase in life expectancy and rising obesity rates, the prevalence of OA continues to grow, placing a substantial burden on healthcare systems and social care infrastructures [1].

Despite being a leading cause of disability in older people, effective long-term management of OA remains a major challenge [3]. Current treatment strategies primarily focus on symptom control, aiming to alleviate pain, improve joint function, and slow disease progression. Non-pharmacological interventions, such as physical therapy and weight management [5], are widely recommended as first-line approaches [3, 6]. However, pharmacological treatments, including analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), and chondroprotective agents, play a crucial role in managing symptoms and preserving the integrity of articular cartilage, particularly in moderate-to-severe OA cases [7].

Among the available pharmacological options, chondroitin sulfate, a natural component of cartilage extracellular matrix, has been extensively studied for its potential

Extended author information available on the last page of the article

disease-modifying and symptom-relieving properties. High quality formulation of SYSADOAs (symptomatic slow-acting drugs for osteoarthritis) at correct dosages has demonstrated chondroprotective and mild anti-inflammatory effects, with evidence suggesting its ability to reduce cartilage degradation and improve joint function [8]. On the other hand, **low dose** diclofenac has been used to give anti-inflammatory action while minimizing systemic adverse effects, making it a valuable option for patients requiring long term use [9].

Although both SYSADOAs and different dosages of diclofenac have individually shown efficacy in OA management, limited evidence exists regarding the potential benefits of their combined use [10]. Given the complementary mechanisms of action—chondroitin sulfate targeting cartilage preservation and diclofenac providing rapid pain relief—there is a strong rationale for evaluating their synergistic effects. However, consensus on their combined efficacy and safety remains undefined, highlighting the need for expert-driven evaluations to guide clinical decision-making.

To address this knowledge gap, a systematic literature review followed by a structured **Delphi survey** was conducted, involving an international Technical Expert Panel (TEP) of OA specialists. The **Delphi method** is a widely used approach for achieving expert consensus through an iterative process of structured questionnaires and controlled feedback [11]. This method is particularly valuable for addressing controversial or emerging topics in medicine where clinical evidence is still evolving. The survey applied the **RAND/UCLA Appropriateness Method**, a validated framework for assessing expert agreement [12], to systematically evaluate the role of the combination in OA treatment.

The primary aim of this TEP was to determine the level of agreement among experts regarding the efficacy, safety, and clinical utility of combining **low dose** diclofenac and chondroitin sulfate in OA management. By analyzing expert consensus, this research seeks to provide clinically relevant insights that may contribute to optimize therapeutic strategies and improve patient outcomes. The findings of this Delphi survey could serve as a foundation for further studies and recommendations in the field of OA treatment.

Materials and methods

The TEP, composed of 5 rheumatologists, 2 orthopedics, 1 specialist in sport medicine, 1 physiatrist, 1 musculoskeletal physiologist and 1 geriatrician, paid great attention to achieve consensus through rigorous scientific methodology.

As part of the Delphi survey, a Systematic Literature Review (SLR) was conducted by S.M.P. (Science Librarian) to examine the use of Condrosulf and Flectorgo in patients with osteoarthritis (OA) and to identify predictors of both positive and negative clinical response.

The steering committee of the TEP including AM (Scientific Coordinator & Steering Committee), ODL, LS, AS, SS and AdS identified the clinical questions for the SLR, formulating them according to the Patient, Problem or Population/Intervention/Comparison, control or comparator/Outcome(s) (PICO) [Timing, duration or date of publication (T)/Study type (S)] format. Table 1 presents the structure of the PICOS research model applied in the review.

To ensure a comprehensive and unbiased selection of literature, the following databases were interrogated: PubMed/Medline, Embase, Cochrane Library. The research exclusively included studies on adult human subjects, without language or publication date restrictions, minimizing the risk of bias due to these factors (Fig. 1). An ad hoc extraction module was developed to systematically collect relevant data from each study. The extraction module captured key study characteristics, including: author, year, type of study, disease and site, type of SYSADOA/NSAID used, number of participants, endpoints, follow-up period, safety and observations [see tables in supplementary material available online].

The retrieved studies were carefully reviewed by the panellists, who selected a subgroup of studies deemed particularly relevant for further assessment. Both quantitative and qualitative syntheses of the extracted data were conducted. The characteristics of the populations enrolled in the selected studies were analyzed.

To ensure the accuracy and reliability of the review process, two independent experts conducted separate evaluations of each study. In cases of discrepancies, a third expert was consulted to reach a final decision. The quality of the selected studies was assessed using the 2018 version of the Mixed Methods Appraisal Tool (MMAT), evaluating key methodological aspects such as study aim appropriateness, research methodology, study design, data collection and analysis methods, and the clarity of reported findings.

The retrieved papers were analyzed and evaluated using a structured data extraction form. The steering committee of the TEP then selected 19 key statements, which were discussed in a first plenary meeting held on web (July 2024).

Table 1 Formulation of clinical questions in PICOS format

PICOS	Human Patients, Adults, Osteoarthritis
I	Oral treatment, diclofenac, NSAID, chondroprotection, Chondroitin sulfate, SYSADOA, combined treatment
C	—
O	All
S	Reviews, Narrative Reviews, Meta-Analysis (11); Randomized Control Trials (6); Prospective studies (2); Retrospective studies (1); Cohort studies (1)

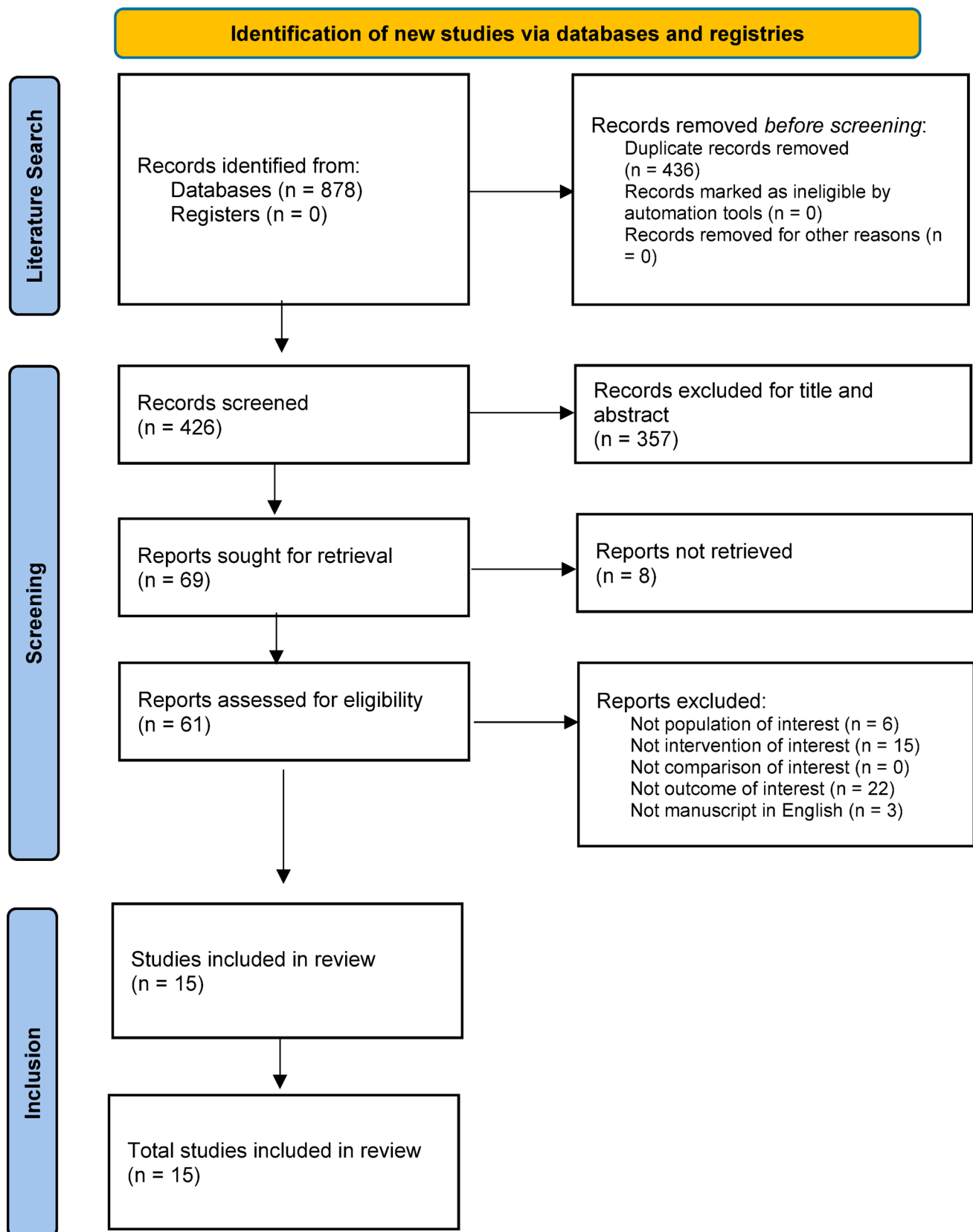


Fig. 1 Selection of paper during the SLR

During a following meeting, the TEP refined the statements, ultimately defining 31 statements, which were further assessed through two rounds of a Delphi survey. The results, including any areas of disagreement, were reviewed and discussed in a final plenary web session in December 2024, where a final consensus was reached.

Results

Considering the results of the SLR, the steering committee proposed 31 statements divided into six domains. During the first TEP meeting, the scientific evidence retrieved was presented and discussed. At the end of the meeting, the TEP defined a questionnaire composed of 33 statements grouped into six domains.

The questionnaire was discussed in two rounds of Delphi survey to find an agreement among the participants. The agreement with each statement was defined according to the RAND/UCLA criteria, with a vote from 1 (total disagreement) to 9 (total agreement). The agreement and disagreement among the experts were defined as follows: agreement if 80% of the 14 panellists' ratings were concentrated in one of the 3-point regions (1–3; 4–6; 7–9); disagreement if 90% of the 14 panellists' ratings were spread across one of the two extra-wide regions (1–6 or 4–9).

The whole process was carried out using a web platform. The results of the questionnaire were discussed by the TEP during the second plenary meeting. Unanimity was reached in the domains, and 33 items (Table 2) were selected.

Overarching considerations

All panellists agree that OA is a multifaceted disease with different phenotypes, as emerging from recent literature [13, 14], and that it requires treatment aimed both at alleviating incident pain and slowing down structural damage [3]. To achieve the latter goal, continuous long-term therapies are necessary, which, due to their prolonged use, must have a high safety profile. This statement is particularly relevant considering that OA patients are often affected by multimorbidity, taking multiple medications, and are of advanced age. Surprisingly, in the first round, there was no strong agreement on the notion that OA is a low-grade inflammatory disease, despite substantial literature spanning the past two decades on the topic [15]. Agreement was reached when the statement was simplified by removing references to disease stages and phenotypes, emphasizing that the inflammatory phenomenon is present across all phenotypes and disease stages.

Rationale of NSAIDs/SYSADOAs combination in knee osteoarthritis

Regarding the rationale for the use of anti-inflammatory drugs and SYSADOAs in knee OA, there is unanimous consensus in considering anti-inflammatory drugs as essential for the OA management. This is clearly reflected in national and international guidelines on knee OA treatment ([16–22]).

While direct comparisons are limited, the overall evidence base for SYSADOAs is considered less robust than that for NSAIDs. Consequently, their use is endorsed mainly by specific international bodies, such as the ESCO [20], while others, such as NICE [23], OARSI [19], and ACR [18], discourage their use. Additionally, some organizations remain uncertain (EULAR [24], SIOT [16], AAOS [21]). However, SYSADOAs have demonstrated an undefined degree of anti-inflammatory, and chondroprotective activity [8, 25, 26] and an optimal safety [27]. Based on this, one of the rationales for using SYSADOAs is to reduce the need for anti-inflammatory drugs [10].

A debated statement concerns whether NSAID constitute a homogeneous class. The initial draft included the phrase “a non-homogeneous class with different relative risks,” based on the review by Magni et al. [22]. This statement reached consensus only after the second Delphi round, following the removal of the final part regarding different relative risks and maintaining “non homogeneous class”.

The last and most comprehensive statement, which immediately reached unanimous agreement, is that the osteoarthritis treatment model includes not only pharmacological therapy, but also physical exercise and rehabilitative interventions aimed at improving joint function. This reflects the multimodal approach endorsed by all scientific societies [19, 20, 23].

Efficacy and safety of low-dose NSAIDs

Regarding the use of low-dose NSAID for disease flares and for prolonged periods in the treatment of osteoarthritic pain, these topics were subject to discussion and were only accepted at the end of the second round of the Delphi process. The combination of disease flares with prolonged treatments did not convince the voters, leading to the separation of the two statements.

During the meetings, attention was focused on two key aspects. First, the goal of controlling pain associated with disease flares using the lowest possible dose of anti-inflammatory drugs [9, 28, 29], a concept endorsed by all international [18, 19] and national [16, 30] guidelines. Second, there was a shared consensus that low-dose anti-inflammatory drugs may be an option for more prolonged periods,

Table 2 Domains and items approved after discussion

Domain	Item	Level of aggregation (%)		
1	Area 1 - Overarching considerations (principles)	% 7–9	% 4–6	% 1–3
1.1	Osteoarthritis (OA) is a multi-form disease with many phenotypes	100,0%	0,0%	0,0%
1.2	In osteoarthritis, a low level of synovial inflammation is present in variable degrees	90,0%	10,0%	0,0%
1.3	In addition to the short-term goals of treating OA (e.g. pain relief and improving musculoskeletal function), it is important to slow down structural damage	90,9%	9,1%	0,0%
1.4	The treatment of OA requires long-lasting and therefore safe therapies	100,0%	0,0%	0,0%
2	Area 2 - Rationale of NSAIDs/SYSADOAs combination in knee osteoarthritis	% 7–9	% 4–6	% 1–3
2.1	NSAIDs are recommended in all guidelines of both international and national societies	90,9%	9,1%	0,0%
2.2	SYSADOAs are recommended in some guidelines of both international and national societies	90,9%	0,0%	9,1%
2.3	The use of SYSADOAs in patients taking systemic NSAIDs is also recommended in order to reduce the consumption of NSAIDs	90,9%	0,0%	9,1%
2.4	Studies on NSAIDs suggest they could not be considered a homogeneous class	100,0%	0,0%	0,0%
2.5	A treatment model including SYSADOAs, NSAIDs, exercise and rehabilitative interventions can be useful to improve joint function	100,0%	0,0%	0,0%
3	Area 3 - Efficacy and safety of low-dose NSAIDs	% 7–9	% 4–6	% 1–3
3.1a	Use of low-dose NSAIDs may be a feasible option for the flare-ups treatment of mild to moderate knee osteoarthritis	90,0%	10,0%	0,0%
3.1b	Use of low-dose NSAIDs may be a feasible option for the prolonged treatment of mild to moderate knee osteoarthritis according to patient's specific factors	90,0%	10,0%	0,0%
3.2	A low-dose regimen of diclofenac ranging from 12.5 to 25 mg per day has been shown to be effective in some clinical trials on musculoskeletal pain	90,0%	10,0%	0,0%
3.3	Common daily doses in clinical practice of oral diclofenac range from 75 to 150 mg	100,0%	0,0%	0,0%
3.6	The safety of low-dosing regimen of diclofenac to control symptoms in osteoarthritis should be considered on an individual patient basis	90,9%	9,1%	0,0%
3.7	Mucosal injury with diclofenac-K liquid 25 mg liquid capsules is significantly lower than ASA 500 mg/day	90,9%	9,1%	0,0%
4	Area 4 - Efficacy and safety of SYSADOAs	% 7–9	% 4–6	% 1–3
4.1	Oral supplementation with pharmaceutical-grade glucosamine or chondroitin sulfate reduces pain in knee OA	81,8%	18,2%	0,0%
4.2	SYSADOAs systemic slow acting drugs for osteoarthritis (chondroitin sulfate, glucosamine, etc.) can be considered safe treatments for patients with knee OA	81,8%	9,1%	9,1%
4.3	Oral supplementation with glucosamine or chondroitin sulfate may improve function in knee OA	81,8%	18,2%	0,0%
4.4	There is clinical evidence suggesting that pharmaceutical grade products of some SYSADOAs (chondroitin and glucosamine) can slow the radiological progression of OA	90,0%	0,0%	10,0%
4.5	Chondroitin sulfate is a potential first-line treatment for the management of patients with mild to moderate OA in knee and/or in other sites	81,8%	9,1%	9,1%
4.6	Efficacy of 800 mg chondroitin sulfate is similar to 200 mg celecoxib in reducing pain and improving function in knee OA patients with radiological Kellgren and Lawrence grade 1–3	90,9%	0,0%	9,1%
5	Area 5 - Efficacy and safety of chondroitin sulfate combined with NSAID in knee OA	% 7–9	% 4–6	% 1–3
5.1	The concomitant use of chondroitin sulfate with NSAID is suggested in order to improve clinical efficacy in patients with knee OA	81,8%	18,2%	0,0%
5.2	Both crystalline glucosamine sulfate and chondroitin sulfate decrease the use of NSAIDs in pharmacoepidemiology studies in patients with knee OA	81,8%	18,2%	0,0%
5.3	The concomitant use of chondroitin sulfate with a NSAID may be cost-effective because the combination reduces the cumulative dose of NSAIDs and related adverse events	90,9%	9,1%	0,0%
6	Area 6 - Efficacy and safety of chondroitin sulfate combined with low-dose diclofenac in knee OA	% 7–9	% 4–6	% 1–3
6.1	Use of Chondroitin Sulfate combined with low-dose diclofenac may contribute to reduce pain in knee OA	90,9%	9,1%	0,0%
6.2	Use of Chondroitin Sulfate combined with low-dose diclofenac allows therapy to be personalized by modulating the NSAID dose according to the patient's inflammatory status and Kellgren-Lawrence grade	90,9%	9,1%	0,0%

but only after an individualized patient assessment. This approach considers the extensive literature on the gastrointestinal and cardiovascular risks associated with long-term use of NSAIDs [31, 32], which can be mitigated by reducing both the dosage of the anti-inflammatory agent [33] and the duration of exposure to the drug.

In line with the objective of this study, further clarification was provided: low-dose diclofenac is defined as a daily dose ranging from 12.5 to 25 mg, whereas the standard dosage of diclofenac ranges from 75 to 150 mg per day.

Finally, it was emphasized that, although low-dose diclofenac represents a therapeutic option with a favorable safety profile compared to other NSAIDs [9, 34], the final decision on prescription should always consider the individual patient's comorbidities.

Efficacy and safety of sysadoas

There is broad, though not unanimous, consensus on the analgesic activity exerted by glucosamine and chondroitin sulfate when administered at a pharmacological dosage [4, 22, 26, 35]. In an initial version that did not specify the pharmacological dosage, several members of the steering committee advocated for its explicit inclusion to distinguish it from a large number of over-the-counter products that do not clearly specify the dosages of their active ingredients [36].

Chondroitin sulfate and glucosamine are considered treatments with a high safety profile, and their oral supplementation may improve knee function in osteoarthritis [37, 38]. There is also evidence suggesting that these compounds may slow the radiographic progression of osteoarthritis [39, 40].

Given these premises, pharmacological-grade chondroitin sulfate, the focus of our research, may represent a first-line treatment option for knee pain in mild to moderate osteoarthritis [40]. Furthermore, there is evidence suggesting that a daily dose of 800 mg of chondroitin sulfate may be comparable to 200 mg of celecoxib in reducing pain associated with mild to moderate knee osteoarthritis [41, 42].

Efficacy and safety of chondroitin sulfate combined with NSAID in knee osteoarthritis

Combining chondroitin sulfate with nonsteroidal anti-inflammatory drugs (NSAIDs) has been explored to enhance clinical efficacy in patients with knee osteoarthritis (OA). Studies suggest that this combination may offer benefits in pain reduction and functional improvement reducing NSAIDs intake [43].

A meta-analysis published in the Archives of Internal Medicine reported that the combination of glucosamine or

chondroitin with NSAIDs at lower cumulative doses than when used alone shows better efficacy in reducing pain associated with OA [44].

The concomitant use of chondroitin sulfate with NSAIDs may be beneficial both clinically and economically for patients with knee OA. This combination could reduce the cumulative dose of NSAIDs required, thereby decreasing the risk of gastrointestinal adverse events associated with NSAID use [10]. Additionally, a cost-effectiveness analysis showed that the use of chondroitin sulfate not only improves clinical symptoms but is also associated with a reduction of overall care costs, primarily due to decreased NSAIDs use and related side effects [10].

Efficacy and safety of chondroitin sulfate combined with low-dose diclofenac in knee osteoarthritis

Given the premises outlined in the previous paragraphs, there has been unanimous consensus from the beginning in considering the combination of a low dose of diclofenac and chondroitin sulfate as beneficial in reducing pain in patients with knee OA [10] despite the lack of literature on this specific topic. In addition to its efficacy, it has also been emphasized that this combination allows for a personalized approach, enabling fine-tuned modulation of the anti-inflammatory dosage administered to each individual patient [45].

Discussion

The Delphi consensus process has confirmed that a combined treatment approach utilizing low-dose NSAIDs and SYSADOAs, particularly chondroitin sulfate, can be both effective and safe for managing knee osteoarthritis. This approach offers the advantage of personalized treatment, allowing clinicians to adjust the anti-inflammatory dosage according to each patient's specific needs. Personalization is crucial in the treatment of OA, as patients may respond differently to medications and exhibit varying tolerances to side effects. This flexibility enables clinicians to optimize treatment efficacy while minimizing the risk of adverse effects. Moreover, combining low-dose NSAIDs with SYSADOAs reduces the need for higher NSAID doses, which are often linked to a higher incidence of adverse events. This is particularly important for OA patients, who often require long-term management of their condition. The combined strategy of low-dose NSAIDs and SYSADOAs may provide an effective treatment option for knee OA, allowing a cumulative effect of the therapeutic target of each one: the control of low-degree inflammation and the protective effect on cartilage. However, further evidence is required

to substantiate this hypothesis. Careful evaluation of each patient's characteristics is essential when initiating therapy to avoid the risks associated with long-term NSAID use in the perspective of the inflammation control along the evolution of the disease. This underscores the importance of personalized medicine in OA management, taking into account each patient's unique needs and potential risks. By integrating both pharmacological treatments with two different products having different mechanism of action and biological target and non-pharmacological treatments, clinicians can optimize patient outcomes while minimizing the risks associated with high dosage of NSAIDs. This whole approach to osteoarthritis management highlights the value of combining multiple treatment modalities to enhance patient outcomes.

The use of SYSADOAs in the treatment of OA remains a subject of ongoing debate within the scientific community. Several issues are currently under discussion. Some efficacy concerns are reported. Some studies suggest that prescription-grade SYSADOAs, such as glucosamine and chondroitin sulfate, may provide pain relief and improve joint function in OA patients. However, the evidence is inconsistent, if you consider RCTs or Meta-analysis involving non-prescription-grade SYSADOAs, these studies report minimal or no benefits compared to placebo [46–48]. There is a wide variability in study results, due to differences in study design, patient populations, and the specific formulations of SYSADOAs. This variability complicates the ability to draw definitive conclusions regarding their effectiveness [49]. Major medical societies, including the American College of Rheumatology (ACR) [18] and the Osteoarthritis Research Society International (OARSI) [19], offer varying guidelines on the use of SYSADOAs. Some recommend their use in certain patient subgroups, while others caution against routine use due to a lack of robust evidence. Other Societies or recommendations like ESCEO [20], EULAR [24], SIOT [16], AAOS [21] recommend SYSADOAs use in the complex OA management. However, it is well recognized that SYSADOAs are generally considered safe, with a low incidence of side effects, which is a favorable aspect, particularly for long-term use in chronic conditions such as OA [27].

Further research is essential to gain a clearer understanding of the potential benefits of SYSADOAs, identify patient subgroups who may benefit most, and determine the optimal dosing and duration of treatment. In summary, while SYSADOAs hold promise for some OA patients, the scientific community agrees that additional high-quality research is needed to solidify their role in clinical treatment guidelines.

However, in this work some limitations must also be acknowledged. The evidence base for the combined use of low-dose diclofenac and chondroitin sulfate remains scarce,

as most clinical studies have investigated these agents separately rather than in combination. As a result, the consensus statements are grounded primarily in indirect evidence and expert opinion, rather than robust randomized controlled trials which are necessary to provide valid scientific evidence. It should also be noted that this consensus was developed by European experts, and recommendations might differ in other regions of the world depending on the availability of active compounds on local markets. In addition, heterogeneity in study designs, patient populations, and SYSADOA formulations across the literature complicates the interpretation and generalizability of findings. Although the Delphi methodology provides a structured and validated process for capturing expert consensus, it is inherently influenced by the panel's composition and prior clinical experience. Finally, the lack of long-term outcome data and comparative effectiveness studies limits the ability to draw firm conclusions regarding durability of effect, safety in multimorbid patients, and cost-effectiveness. These limitations highlight the need for well-designed, adequately powered clinical trials to substantiate the preliminary consensus reached in this study.

Nevertheless, the group of international experts consulted on this issue has provided a clear and unanimous recommendation, suggesting it as a potential first-line treatment for mild-to-moderate knee osteoarthritis. Given the increasing average age of the population and the growing burden of comorbidities, this option, while not supported by robust scientific evidence, appears to have a rational basis for use.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s40520-025-03221-2>.

Acknowledgements We would like to express our gratitude to Alessandro Urbani (Methodologist – Venice, Italy) and Paolo Sarais (Science Librarian – Rome, Italy) for their valuable contributions and support throughout the development of this project.

Author contributions All authors contributed to data analysis, drafting or revising the article, gave final approval for the version to be published, agreed to the submitted journal, and agreed to be accountable for all aspects of the work.

Funding The publication of this article was supported by a non-conditioning grant from IBSA International (Lugano, Switzerland). The participation of JYR to this work has been supported by the DSFP of King Saud University, Riyadh, Kingdom of Saudi Arabia.

Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests JYR has received consultancy fees and speaker bureau's honorarium from IBSA; LS was supported by MHCR

023728; all other authors declare no conflict of interests.

Disclosure JYR has received consultancy fees and speaker bureau's honorarium from IBSA; LS was supported by MHCR 023728; all other authors declare no conflict of interests.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

References

1. Tang S, Zhang C, Oo WM et al (2025) Osteoarthritis. *Nat Rev Dis Primers* 11:10. <https://doi.org/10.1038/S41572-025-00594-6>
2. Luo Q, Zhang S, Yang Q et al (2024) Causal factors for osteoarthritis risk revealed by Mendelian randomization analysis. *Aging Clin Exp Res* 36. <https://doi.org/10.1007/S40520-024-02812-9>
3. Kloppenburg M, Namane M, Cicuttini F (2025) Osteoarthritis. *Lancet* 405:71–85. [https://doi.org/10.1016/S0140-6736\(24\)02322-5](https://doi.org/10.1016/S0140-6736(24)02322-5)
4. Herrero-Beaumont G, Castro-Dominguez F, Migliore A et al (2024) Systemic osteoarthritis: the difficulty of categorically naming a continuous condition. *Aging Clin Exp Res* 36. <https://doi.org/10.1007/S40520-024-02714-W>
5. Veronese N, Ragusa FS, Dominguez LJ et al (2024) Mediterranean diet and osteoarthritis: an update. *Aging Clin Exp Res* 36:231. <https://doi.org/10.1007/s40520-024-02883-8>
6. Wen Z, Chen Q, Lan X et al (2025) Physical modalities for the treatment of knee osteoarthritis: a network meta-analysis. *Syst Rev Aging Clin Experimental Res* 37:121. <https://doi.org/10.1007/s40520-025-03015-6>
7. Gallagher B, Tjoumakaris FP, Harwood MI et al (2015) Chondroprotection and the prevention of osteoarthritis progression of the knee: a systematic review of treatment agents. *Am J Sports Med* 43:734–744. <https://doi.org/10.1177/0363546514533777>
8. Reginster JY, Veronese N (2021) Highly purified chondroitin sulfate: a literature review on clinical efficacy and Pharmacoeconomic aspects in osteoarthritis treatment. *Aging Clin Exp Res* 33:37–47. <https://doi.org/10.1007/S40520-020-01643-8>
9. Trevisan CLM, Carraro A, Baldari GLA (2023) Treatment Satisfaction, Efficacy, and tolerability of Low-Dose diclofenac epolamine soft capsules in Acute, Mild, or moderate musculoskeletal pain: A prospective Open-Label, Single-Arm interventional study. *Pain Ther* 12:1149–1163. <https://doi.org/10.1007/S40122-023-00531-Z>
10. Rubio-Terrés C (2010) [An economic evaluation of chondroitin sulfate and non-steroidal anti-inflammatory drugs for the treatment of osteoarthritis. Data from the VECTRA study]. *Reumatol Clin* 6:187–195. <https://doi.org/10.1016/J.REUMA.2009.12.009>
11. Sablatzky T (2022) The Delphi method. Hypothesis: *Res J Health Inform Professionals* 34(2022). <https://doi.org/10.18060/26224>
12. Sparks JB, Klamers ML, Caverly TJ et al (2022) Planning and reporting effective Web-Based RAND/UCLA appropriateness method panels: literature review and preliminary recommendations. *J Med Internet Res* 24:e33898. <https://doi.org/10.2196/33898>
13. Deveza LA, Melo L, Yamato TP et al (2017) Knee osteoarthritis phenotypes and their relevance for outcomes: a systematic review. *Osteoarthritis Cartilage* 25:1926–1941. <https://doi.org/10.1016/J.JOCA.2017.08.009>
14. Deveza LA, Nelson AE, Loeser RF (2019) Phenotypes of osteoarthritis - current state and future implications. *Clin Exp Rheumatol* 37:64
15. Scanzello CR (2017) Role of low-grade inflammation in osteoarthritis. *Curr Opin Rheumatol* 29:79–85. <https://doi.org/10.1097/BOR.0000000000000353>
16. Pesare E, Vicenti G, Kon E et al (2023) Italian orthopaedic and traumatology society (SIOT) position statement on the non-surgical management of knee osteoarthritis. *J Orthop Traumatol* 24:47. <https://doi.org/10.1186/s10195-023-00729-z>
17. Jordan KM, Arden NK, Doherty M et al (2003) EULAR recommendations 2003: an evidence based approach to the management of knee osteoarthritis: report of a task force of the standing committee for international clinical studies including therapeutic trials (ESCSIT). *Ann Rheum Dis* 62:1145–1155. <https://doi.org/10.1136/ARD.2003.011742>
18. Kolasinski SL, Neogi T, Hochberg MC et al (2020) 2019 American college of Rheumatology/Arthritis foundation guideline for the management of osteoarthritis of the Hand, Hip, and knee. *Arthritis Care Res (Hoboken)* 72:149–162. <https://doi.org/10.1002/ACR.24131/ABSTRACT>
19. Bannuru RR, Osani MC, Vaysbrot EE et al (2019) OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. *Osteoarthritis Cartilage* 27:1578–1589. <https://doi.org/10.1016/J.JOCA.2019.06.011>
20. Bruyère O, Honvo G, Veronese N et al (2019) An updated algorithm recommendation for the management of knee osteoarthritis from the European society for clinical and economic aspects of Osteoporosis, osteoarthritis and musculoskeletal diseases (ESCEO). *Semin Arthritis Rheum* 49:337–350. <https://doi.org/10.1016/J.SEMARTHRT.2019.04.008>
21. Brophy RH, Fillingim YA (2022) AAOS clinical practice guideline summary: management of osteoarthritis of the knee (Nonarthroplasty), third edition. *J Am Acad Orthop Surg* 30:E721–E729. <https://doi.org/10.5435/JAAOS-D-21-01233>
22. Conrozier T, Diraçoglu D, Monfort J et al (2023) EUROVISCO good practice recommendations for a first viscosupplementation in patients with knee osteoarthritis. *Cartilage* 14:125–135. <https://doi.org/10.1177/19476035221138958>
23. Overview | Osteoarthritis in over 16s: diagnosis and management | Guidance | NICE
24. Fernandes L, Hagen KB, Bijlsma JWJ et al (2013) EULAR recommendations for the non-pharmacological core management of hip and knee osteoarthritis. *Ann Rheum Dis* 72:1125–1135. <https://doi.org/10.1136/ANNRHEUMDIS-2012-202745>
25. Clegg DO, Reda DJ, Harris CL et al (2006) Glucosamine, chondroitin Sulfate, and the two in combination for painful knee osteoarthritis. *N Engl J Med* 354:795–808. https://doi.org/10.1056/NEJMOA052771/ASSET/6840B307-E375-4F2A-875D-878A8A9CE33C/ASSETS/IMAGES/LARGE/NEJMOA052771_F3.JPG
26. Simental-Mendía M, Sánchez-García A, Vilchez-Cavazos F et al (2018) Effect of glucosamine and chondroitin sulfate in symptomatic knee osteoarthritis: a systematic review and meta-analysis of randomized placebo-controlled trials. *Rheumatol Int* 38:1413–1428. <https://doi.org/10.1007/S00296-018-4077-2>
27. Honvo G, Reginster JY, Rabenda V et al (2019) Safety of symptomatic Slow-Acting drugs for osteoarthritis: outcomes of a systematic review and Meta-Analysis. *Drugs Aging* 36:65–99. <https://doi.org/10.1007/S40266-019-00662-Z>

28. Kienzler JL, Gold M (2012) Diclofenac potassium 12.5 mg liquid capsules: earlier and higher exposure to diclofenac. A fasted, single-dose, comparative, bioavailability study versus diclofenac potassium 12.5 mg tablets. *Int J Clin Pharmacol Ther* 50:438–444. <https://doi.org/10.5414/CP201641>
29. Zuniga JR, Noveck RJ, Schmidt WK et al (2011) Onset of action of diclofenac potassium liquid-filled capsules in dental surgery patients. *Curr Med Res Opin* 27:1733–1739. <https://doi.org/10.1185/03007995.2011.600300>
30. Ariani A, Manara M, Fioravanti A et al (2019) The Italian society for rheumatology clinical practice guidelines for the diagnosis and management of knee, hip and hand osteoarthritis. *Reumatismo* 71:5–21. <https://doi.org/10.4081/REUMATISMO.2019.1188>
31. Bally M, Dendukuri N, Rich B et al (2017) Risk of acute myocardial infarction with NSAIDs in real world use: bayesian meta-analysis of individual patient data. *BMJ* 357. <https://doi.org/10.1136/BMJ.J1909>
32. Lanas A, Chan FKL (2017) Peptic ulcer disease. *Lancet* 390:613–624. [https://doi.org/10.1016/S0140-6736\(16\)32404-7](https://doi.org/10.1016/S0140-6736(16)32404-7)
33. Moore N (2007) Diclofenac potassium 12.5 mg tablets for mild to moderate pain and fever: a review of its pharmacology, clinical efficacy and safety. *Clin Drug Investig* 27:163–195. <https://doi.org/10.2165/00044011-200727030-00002>
34. Pelletier JP, Martel-Pelletier J, Rannou F, Cooper C (2016) Efficacy and safety of oral NSAIDs and analgesics in the management of osteoarthritis: evidence from real-life setting trials and surveys. *Semin Arthritis Rheum* 45:S22–S27. <https://doi.org/10.1016/J.SEMARTHRT.2015.11.009>
35. Zhu X, Sang L, Wu D et al (2018) Effectiveness and safety of glucosamine and chondroitin for the treatment of osteoarthritis: A meta-analysis of randomized controlled trials. *J Orthop Surg Res* 13. <https://doi.org/10.1186/S13018-018-0871-5>
36. Volpi N (2009) Quality of different chondroitin sulfate preparations in relation to their therapeutic activity. *J Pharm Pharmacol* 61:1271–1280. <https://doi.org/10.1211/JPP.61.10.0002>
37. Rabade A, Viswanatha GL, Nandakumar K, Kishore A (2024) Evaluation of efficacy and safety of glucosamine sulfate, chondroitin sulfate, and their combination regimen in the management of knee osteoarthritis: a systematic review and meta-analysis. *Inflammopharmacology* 32:1759–1775. <https://doi.org/10.1007/S10787-024-01460-9>
38. Hochberg MC, Martel-Pelletier J, Monfort J et al (2016) Combined chondroitin sulfate and glucosamine for painful knee osteoarthritis: A multicentre, randomised, double-blind, non-inferiority trial versus celecoxib. *Ann Rheum Dis* 75:37–44. <https://doi.org/10.1136/ANNRHEUMDIS-2014-206792/-/DC1>
39. Lee YH, Woo JH, Choi SJ et al (2010) Effect of glucosamine or chondroitin sulfate on the osteoarthritis progression: a meta-analysis. *Rheumatol Int* 30:357–363. <https://doi.org/10.1007/S00296-009-0969-5>
40. Hochberg MC (2010) Structure-modifying effects of chondroitin sulfate in knee osteoarthritis: an updated meta-analysis of randomized placebo-controlled trials of 2-year duration. *Osteoarthritis Cartilage* 18:S28–S31. <https://doi.org/10.1016/j.joca.2010.02.016>
41. Bruyère O (2018) Pharmaceutical-grade chondroitin sulfate in the management of knee osteoarthritis. *Expert Opin Pharmacother* 19:409–412. <https://doi.org/10.1080/14656566.2018.1442438>
42. Reginster JY, Dudler J, Blicharski T, Pavelka K (2017) Pharmaceutical-grade chondroitin sulfate is as effective as celecoxib and superior to placebo in symptomatic knee osteoarthritis: the chondroitin versus celecoxib versus placebo trial (CONCEPT). *Ann Rheum Dis* 76:1537–1543. <https://doi.org/10.1136/ANNRHEUMDIS-2016-210860>
43. Cho SK, Kim H, Park HR et al (2019) Nonsteroidal Anti-inflammatory drugs-sparing effect of symptomatic Slow-acting drugs for osteoarthritis in knee osteoarthritis patients. *J Rheumatic Dis* 26:179–185. <https://doi.org/10.4078/JRD.2019.26.3.179>
44. Richey F, Bruyere O, Ethgen O et al (2003) Structural and symptomatic efficacy of glucosamine and chondroitin in knee osteoarthritis: A comprehensive Meta-analysis. *Arch Intern Med* 163:1514–1522. <https://doi.org/10.1001/ARCHINTE.163.13.1514>
45. Veronese N, Ecarnot F, Cheleschi S et al (2022) Possible synergic action of non-steroidal anti-inflammatory drugs and glucosamine sulfate for the treatment of knee osteoarthritis: a scoping review. *BMC Musculoskelet Disord* 23:1–9. <https://doi.org/10.1186/S12891-022-06046-6/TABLES/1>
46. Wandel S, Jüni P, Tendal B et al (2010) Effects of glucosamine, chondroitin, or placebo in patients with osteoarthritis of hip or knee: network meta-analysis. *BMJ* 341:711. <https://doi.org/10.1136/BMJ.C4675>
47. Wu D, Huang Y, Gu Y, Fan W (2013) Efficacies of different preparations of glucosamine for the treatment of osteoarthritis: a meta-analysis of randomised, double-blind, placebo-controlled trials. *Int J Clin Pract* 67:585–594. <https://doi.org/10.1111/IJCP.12115>
48. Miller KL, Clegg DO (2011) Glucosamine and chondroitin sulfate. *Rheumatic Disease Clin North Am* 37:103–118. <https://doi.org/10.1016/J.RDC.2010.11.007>
49. Vitaloni M, Möller I, Verges J (2021) SYSADOAs: Su Origen y Calidad Hacen La diferencia En eficacia y seguridad? *Global Rheumatol*. <https://doi.org/10.46856/GRP.10.E072>

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Authors and Affiliations

Alberto Migliore¹  · Orazio De Lucia²  · Alessandro de Sire^{3,4}  · Andrea Šajbidor^{5,6}  · Ladislav Šenolt^{7,8} ·
Sándor Szántó⁹  · Joan Calvet Fontova¹⁰  · Johannes Flechtenmacher¹¹  · Ali Mobasher^{12,13,14}  ·
Jordi Monfort Faure¹⁵  · Jean-Yves Reginster¹⁶  · Nicola Veronese^{17,18} 

✉ Orazio De Lucia
orazio.delucia@asst-pini-cto.it

¹ Rheumatology Unit, San Pietro Fatebenefratelli Hospital, Rome, Italy

² Department of Rheumatology and Medical Sciences, Clinical Rheumatology Unit, ASST Gaetano Pini-CTO, Milan, Italy

³ Physical and Rehabilitative Medicine, Department of Medical and Surgical Sciences, University of Catanzaro “Magna Graecia”, Catanzaro 88100, Italy

⁴ Research Center on Musculoskeletal Health, MusculoSkeletalHealth@UMG, University of Catanzaro “Magna Graecia”, Catanzaro 88100, Italy

⁵ Špecializovaná Nemocnica Pre Ortopedickú Protetiku, Záhradnícka 42, Bratislava 821 08, Slovakia

⁶ Orthopedic Clinic, Bratislava, Slovakia

⁷ Institute of Rheumatology, Na Slupi 4, Prague 128 00, Czech Republic

⁸ Department of Rheumatology, First Faculty of Medicine, Charles University, Prague, Czech Republic

⁹ Faculty of Medicine, Department of Sports Medicine, University of Debrecen, Debrecen, Hungary

¹⁰ Department of Rheumatology, Medicine Department, Parc Taulí Hospital Universitari, Institut d'Investigació i Innovació Parc Taulí (I3PT-CERCA), Universitat Autònoma de Barcelona, Sabadell, Spain

¹¹ Ortho-Zentrum Karlsruhe, Waldstrasse 67, 76133 Karlsruhe, Germany

¹² Research Unit of Health Sciences and Technology, Physics and Technology, University of Oulu, Oulu, Finland

¹³ Department of Regenerative Medicine, State Research Institute Centre for Innovative Medicine, Vilnius, Lithuania

¹⁴ Department of Joint Surgery, Sun Yat-sen University, Guangzhou, People's Republic of China

¹⁵ Department of Rheumatology, Institut Hospital del Mar d'Investigacions Mèdiques, Passeig Marítim de la Barceloneta, 25, 29, 08003 Barcelona, Spain

¹⁶ Protein Research Chair, Biochemistry Department, College of Science, King Saud University, Riyadh, Kingdom of Saudi Arabia

¹⁷ Saint Camillus International University of Health Sciences, Rome, Italy

¹⁸ Unità Locale Socio Sanitaria 3 Serenissima, Primary Care Department, Dolo Mirano, Venice, Italy