Chondroprotection and the Prevention of Osteoarthritis Progression of the Knee

CME

A Systematic Review of Treatment Agents

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Background: Structure-modifying medications or nutraceuticals may be an effective treatment for osteoarthritis. This study identified 12 treatments that may possess chondroprotective properties: oral glucosamine; chondroitin; nonsteroidal anti-inflammatory drugs (NSAIDs); polyunsaturated fatty acids; S-adenosylmethionine; avocado and soybean unsaponifiable fractions; methylsulfonylmethane; vitamins C, D, and E; intra-articular injections of hyaluronic acid; and platelet-rich plasma (PRP).

Purpose: To perform a systematic review of randomized controlled trials for the effectiveness of each agent in preserving articular cartilage of the knee and delaying the progression of osteoarthritis.

Study Design: Systematic review; Level of evidence, 2.

Methods: A literature search was performed using PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials. Searches were performed using ''treatment,'' ''osteoarthritis,'' and ''knee'' as keywords. Selection criteria included randomized controlled trials of $\geq$12 months, with a placebo control, measuring radiographic changes in joint space width, cartilage volume, or radiographic progression of osteoarthritis. The primary outcome was changes in joint integrity measures.

Results: A total of 3514 studies were identified from the initial search, 13 of which met inclusion criteria. Treatment with chondroitin sulfate showed a significant reduction in cartilage loss in 3 of 4 studies identified compared with placebo. Two of 3 trials identified for glucosamine also reported significant structural effects relative to placebo. Intra-articular hyaluronic acid was effective in lowering the rate of cartilage loss in only 1 of 3 studies identified versus placebo. Of the 6 studies identified for NSAIDs, vitamin E, and vitamin D, none showed any structural effect compared with placebo. No studies were found that met the inclusion criteria for polyunsaturated fatty acids, S-adenosylmethionine, avocado and soybean unsaponifiable fractions, methylsulfonylmethane, vitamin C, or PRP.

Conclusion: For patients with or at risk for osteoarthritis, the use of glucosamine and chondroitin sulfate may serve as a nonoperative means to protect joint cartilage and delay osteoarthritis progression. Hyaluronic acid injections showed variable efficacy, while NSAIDs and vitamins E and D showed no effect on osteoarthritis progression. The other agents evaluated had no evidence in the literature to support or refute their use for chondroprotection.

Keywords: knee; articular cartilage; chondroprotection; nutraceutical

Osteoarthritis (OA) is a major cause of musculoskeletal pain and disability worldwide.[46] It affects an estimated 27 million Americans at a total approximate cost of US$185.5 billion per year.[21,22] Structural changes seen in patients suffering from OA are characterized by a progressive loss of joint articular cartilage and subchondral bone lesions.[2,33] The pathophysiology of OA involves the complex interaction of mechanical stress, oxidative damage, and inflammatory mediators and the catabolic-anabolic balance of the joint, synovium, matrix, and chondrocytes.[13,27,38,41] Both acute and chronic mechanisms contribute to the progressive loss of articular cartilage seen in OA.

Currently, treatment focuses mostly on alleviating the symptoms of the disease rather than modifying the disease process. Pharmacological agents capable of altering the catabolic and anabolic balance of the joint are of particular interest for their potential as structure-modifying drugs.

The following 12 agents have been studied for their potential "chondroprotective" properties: oral glucosamine; chondroitin sulfate; nonsteroidal anti-inflammatory drugs (NSAIDs); polyunsaturated fatty acids; S-adenosylmethionine; avocado and soybean unsaponifiable fractions;

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The authors declared that they have no conflicts of interest in the authorship and publication of this contribution.

The American Journal of Sports Medicine, Vol. 43, No. 3
DOI: 10.1177/0363546514533777

methylsulfonylmethane; vitamins C, D, and E; intra-articular injections of hyaluronic acid; and platelet-rich plasma (PRP).[7,23,25,26,37,46] The purpose of this study was to perform a systematic review of the literature to determine if there was any high-level evidence that supports the routine use of these agents to modify the disease process of OA.

MATERIALS AND METHODS

Identification of Therapeutic Agents to Investigate

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were followed from the inception of the study. The 12 treatment agents identified for inclusion in this study and listed above were determined by an initial literature search of trials and reviews discussing the nonsurgical treatment of knee OA. We focused on identifying pharmaceutical treatments recognized as possessing potential structure-modifying, chondroprotective properties of the joint. Particularly, we sought to identify potential treatments associated with halting or positively influencing the progression of OA. Any agents that were not initially included and were identified after a further literature review were searched individually as well.

Identification of Eligible Studies

We sought to identify all randomized controlled trials with a minimum of 12 months' follow-up that evaluated each treatment agent's ability to effect changes in knee joint structure. Searches of PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials were performed from their respective inceptions through June 2013. Each search was performed using "treatment," "osteoarthritis," and "knee" as keywords. In the case of NSAIDs, the terms "NSAID" and "non-steroidal anti-inflammatory" were used in addition to specific drug names; terms included "piroxicam," "diclofenac," "celecoxib," "naproxen," "ibuprofen," and "diacerein." All references from selected studies were reviewed to identify any additional articles that may have been overlooked or were not indexed in the electronic databases. Selection criteria included randomized controlled trials of $\geq$12 months, with a placebo control, that measured structural changes associated with OA of the knee. We chose to include only those studies with a placebo control to make more accurate comparisons between studies and to draw conclusions about absolute rather than relative efficacy. Measures included changes in joint space width (JSW), the distance between the femoral condyle and tibial plateau; or joint space narrowing, the change in JSW, measured by established radiographic criteria; or changes in cartilage volume, measured by magnetic resonance imaging (MRI). All measures have been validated in the assessment of cartilage degeneration and OA progression.[3,6,45] Reasons for exclusion are listed in Figure 1.

Data Extraction

Information was extracted according to a predetermined form; data collected included the following: treatment modality and course, duration of study, population demographics, intention-to-treat analysis, initial injury, sample sizes, baseline Kellgren-Lawrence score, change in JSW or cartilage volume, number of patients who experienced a progression of OA, and change in pain scores using either the Western Ontario and McMaster Universities Arthritis Index (WOMAC) or visual analog scale (VAS) for pain.[20]

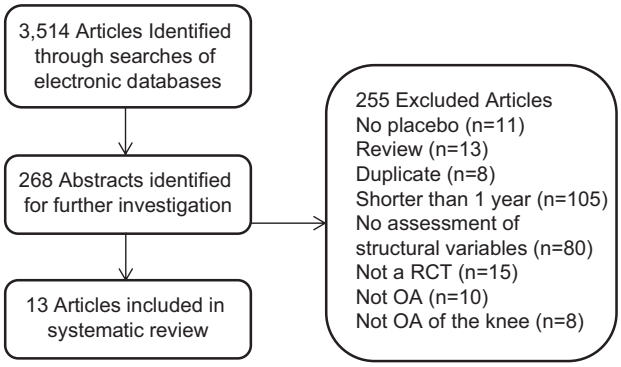

Figure 1. Flowchart diagramming the inclusion and exclusion of identified studies. RCT, randomized controlled trial; OA, osteoarthritis.

The Kellgren-Lawrence score is a grade of increasing severity of knee pathological lesions from 0 to 4 based on the presence of osteophytes, joint space loss, subchondral sclerosis, and the presence of cysts.[39] The WOMAC scores are based on the results of a 24-part disease-specific questionnaire that assesses pain, stiffness, and function, with a maximal score of 2400 mm indicating severe disease. The pain subscale accounts for 200 of the 2400 mm but can be normalized to ranges from 0 to 100 or 0 to 25 in studies using the Likert scale variation.[32] The VAS grades pain on a scale of 0 to 100 mm (100 indicating worst pain) based on a patient questionnaire.[36]

Means $\pm$ SDs and 95% CIs were extracted. When rates of OA progression were provided, we calculated the odds ratio of experiencing joint space narrowing according to the study's indicated threshold for progression. Industry involvement was noted when reported. Primary outcome measures analyzed were the change in JSW or cartilage volume from baseline to completion of the study. The secondary outcome measure investigated was the change in pain symptoms according to the total WOMAC score, WOMAC pain subscore, or VAS pain score. We evaluated each study for potential sources of bias within and among studies including adequate sequence generation, allocation concealment, blinding, presence of incomplete outcome data, presence of selective reporting, industry participation, and any other biases. Scientific quality was appraised using the Jadad scoring system, which grades scientific quality from 0 to 5 based on the presence of appropriate blinding and randomization in addition to reporting of incomplete outcome data.[17] Two points are given for studies described as randomized and blinded. Additional points are given or subtracted based on study protocols.[7]

TABLE 1
Characteristics of Studies Included in the Systematic Review[a]

							Baseline Characteristics			Withdrawal Rate	
Study	Intervention	Dose	Duration, mo	ITT Analysis	Structural Variables	No. of Patients	Mean Age, y	Female, %	Mean BMI, kg/m^2	Treatment, %	Placebo, %
Chondroitin											
Kahan et al[19]	Chondroitin sulfate	800 mg/d	24	Yes	Minimum JSW	622	62.8	77.0	NS	26.7	27.3
Michel et al[31]	Chondroitin sulfate	800 mg/d	24	Yes	Mean and minimum JSW	300	62.3	68.3	28.6	30.7	33.3
Sawitzke et al[39]	Chondroitin sulfate	400 mg 3 times/d	24	Yes	Minimum JSW	257	56.9	63.6	32.0	28.0	31.5
Uebelhart et al[40]	Chondroitin sulfate	800 mg/d for 2 periods of 3 mo	12	Yes	Mean and minimum JSW	120	63.5	80.9	NS	20.4	26.8
Glucosamine											
Reginster et al[36]	Glucosamine sulfate	1500 mg/d	36	Yes	Mean and minimum JSW	212	65.8	76.5	27.4	33.00	35.80
Pavelka et al[32]	Glucosamine sulfate	1500 mg/d	36	Yes	Mean and minimum JSW	202	62.4	78.5	25.7	34.70	45.50
Sawitzke et al[39]	Glucosamine hydrochlorate	500 mg 3 times/d	24	Yes	Minimum JSW	268	56.9	63.6	32.0	27.7	31.5
Hyaluronic acid											
Wang et al[43]	Hylan G-F 20 (6000 kDa)	4 courses: once weekly for 3 wk; 6 mo between courses	24	Yes	Medial and lateral tibiofemoral cartilage volumes	78	61.4	47.0	29.5	35.9	23.1
Pham et al[34]	NRD101 (1.9 kDa)	3 courses: once weekly for 3 wk; 6 mo between courses	12	Yes	Mean and minimum JSW	216	64.8	69.7	NS	6.90	5.90
Listrat et al[24]	Hyalgan (500-730 kDa)	3 courses: once weekly for 3 wk; 6 mo between courses	12	Yes	Mean and minimum JSW, VAS, and SFA structural scales	39	61.9	66.7	27.1	5.00	10.50
Vitamin D											
McAlindon et al[30]	Vitamin D	2000 IU/d	24	Yes	Mean JSW, tibiofemoral cartilage volume	146	62.4	60.5	30.7	12.3	17.8
Vitamin E											
Wluka et al[44]	Vitamin E	500 IU/d	24	Yes	Tibiofemoral cartilage volume	136	64.0	55.3	29.1	7.80	6.50
NSAIDs											
Dieppe et al[10]	Diclofenac	100 mg/d	24	Yes	Mean JSW	150	63.1	65.0	NS	31.1	54.5
Buckland-Wright et al[6]	Diclofenac	100 mg/d	18	Yes	Minimum JSW	45	65.5	72.7	NS	27.2	26.1
Pham et al[34]	Diacerein	50 mg/d	12	Yes	Mean and minimum JSW	170	64.7	65.3	NS	5.90	5.90
Sawitzke et al[39]	Celecoxib	200 mg/d	24	Yes	Minimum JSW	277	56.9	63.6	32.0	26.2	31.5

[a]BMI, body mass index; ITT, intention to treat; JSW, joint space width; NS, not stated; NSAID, nonsteroidal anti-inflammatory drug; SFA, French Society of Arthroscopy; VAS, visual analog scale.

Data Synthesis

Data were ordered by treatment modality and organized to make comparisons and draw conclusions of treatment efficacy when possible. To draw positive conclusions, we looked for clear, consistent, and replicated evidence from high-quality studies of an association between a treatment and a change in either primary or secondary outcome measures compared with placebo. Because of differences among treatment protocols, dosage strategies, structural variables measured, and medications, we decided against pooling data for a meta-analysis.

Source of Funding

We received no external sources of funding in the generation of this review.

RESULTS

Identification of Eligible Studies

An initial literature search yielded 3514 references. Of these, 268 articles were selected based on the title for further investigation. Abstracts and whole articles were read to determine if the study met inclusion criteria. Of the 268 articles reviewed, we identified 13 articles that fulfilled our criteria (Figure 1).

Four studies were identified for chondroitin sulfate, 3 for glucosamine, 3 for hyaluronic acid injections, 1 for vitamin D, 1 for vitamin E, and 4 for NSAIDs. Two studies, Sawitzke et al[39] and Pham et al,[34] met the inclusion criteria for multiple agents and are listed multiple times. Characteristics of the studies are summarized in Table 1.

We were unable to identify any articles that met the inclusion criteria for polyunsaturated fatty acids, S-adenosylmethionine, avocado and soybean unsaponifiable fractions, methylsulfonylmethane, vitamin C, or intra-articular injections of PRP.

Measurement of JSW and Cartilage Volume

Table 2 summarizes the methods in which JSW and cartilage volume were determined in each study as well as any interobserver and intraobserver variability between radiographs that were reported. Studies that determined JSW using computerized methods followed a protocol that in general called for the digitization of radiographs. This was followed by $\geq$1 blinded observers using a computer

TABLE 2
Method for Measurement of Structural Variables and Reported Variability[a]

Study	Variable Measured	Calculation Method	No. of Observers	Reported Variability
Kahan et al[19]	JSW	Computerized	2	Interobserver CC = 0.9886
Michel et al[31]	JSW	Computerized	2	Interclass CC = 0.98
Sawitzke et al[39]	JSW	Computerized	2	Standard error = 0.025 mm
Uebelhart et al[40]	JSW	Computerized	2	None reported
Reginster et al[36]	JSW	Computerized	2	Mean ± SD CoV = 1.82 ± 1.29 (short term) and 1.62 ± 1.31 (long term)
Pavelka et al[32]	JSW	Observer with 0.1-mm graduated magnifying glass	2	Interobserver CoV = 2.53
Wang et al[43]	Cartilage volume	Computerized	2	CoV = 3.4 (medial) and 2.0 (lateral)
Pham et al[34]	JSW	Observer with 0.1-mm graduated magnifying glass	2	Interobserver interclass CC = 0.912 (95% CI, 0.887-0.931), intraobserver CC = 0.996 (95% CI, 0.991-0.998), intraclass CC = 0.922 (95% CI, 0.989-0.966)
Listrat et al[24]	JSW	Observer with 0.1-mm graduated magnifying glass	1	None reported
McAlindon et al[30]	JSW	Computerized	1	None reported
	Cartilage volume	Computerized	2	Intraobserver CoV = 1.7 (tibial) and 1.4 (femoral) Interacquisition CoV = 3.9 (tibial) and 1.3 (femoral)
Wluka et al[44]	Cartilage volume	Computerized	2	CoV = 2.6 (total), 3.4 (medial), and 2.0 (lateral)
Dieppe et al[10]	JSW	Computerized	1	None reported
Buckland-Wright et al[6]	JSW	Computerized	2	CoV = 1.2

[a]CC, correlation coefficient; CI, confidence interval; CoV, coefficient of variability; JSW, joint space width; SD, standard deviation.

to place vertical lines demarcating the boundaries of the joint to be read. A computer would then use these lines to automatically calculate the mean JSW and/or minimum JSW within the compartment.[6,10,19,30,31,36,39,40] Pavelka et al,[32] Pham et al,[34] and Listrat et al[24] did not use a computerized method. Rather, they determined JSW directly by measuring radiographs with a magnifying glass graduated in 0.1-mm intervals (Table 2). Cartilage volume was calculated using computerized methods. Blinded observers were used to manually draw borders around areas of cartilage on digitized MRI slides. These images were then collected and analyzed in 3-dimension by software, which calculated the cartilage volume.[30,43,44]

Effect of Chondroitin on JSW, OA Progression, and Pain

Four trials were identified that assessed knee JSW and OA progression after treatment with chondroitin sulfate for a mean duration of 21 months.[19,31,39,40] Study populations showed similar baseline characteristics and withdrawal rates between the intervention and placebo groups (Table 1). Patient populations represented those diagnosed with primary OA according to American College of Rheumatology criteria that was confirmed to not be secondary to any pre-existing condition.[2,19,31,39,40] The diagnosis was based on a progressive algorithm with the presence of knee pain as well as clinical and laboratory data including age, morning stiffness, crepitus, bony tenderness and enlargement, palpable warmth, erythrocyte sedimentation rate, and rheumatoid factor and synovial fluid tests.[2] Patients were evaluated for Kellgren-Lawrence grading before entry (Table 3). No study showed baseline differences between the intervention and placebo groups. Dosage strategies differed slightly (Table 1). Kahan et al,[19] Michel et al,[31] and Uebelhart et al[40] administered 800 mg daily. However, in the Uebelhart et al[40] study, patients received treatment in two 3-month cycles at the beginning of the study and at 6 months. Sawitzke et al[39] prescribed 400 mg 3 times daily. All studies received a Jadad score of 5 for scientific quality and showed no major identifiable sources of bias (Table 4). Kahan et al,[19] Michel et al,[31] and Uebelhart et al[40] were determined to have received industry support.

Three studies noted significant structure-modifying effects of treatment with chondroitin sulfate compared with placebo. The progression of OA was defined as a decrease in JSW of 0.50 mm by Kahan et al,[19] Michael et al,[31] and Uebelhart et al[40] and 0.48 mm by Sawitzke et al.[39] Loss of mean JSW, reported by Michel et al[31] and Uebelhart et al,[40] was found to be significantly reduced in the chondroitin sulfate groups compared with those receiving placebo by 0.14 mm (95% CI, 0.01-0.27; $P = .04$) and 0.28 mm (95% CI, 0.01-0.55; $P = .04$), respectively (Table 5). Reduction of minimum JSW, reported by all 4 studies, was significantly decreased in the chondroitin

TABLE 3
Kellgren-Lawrence Scores at Baseline of Study Populations[a]

Study	Kellgren-Lawrence Grade, %			
	1	2	3	4
Chondroitin				
Kahan et al[19]	18.50	23.90	57.60	—
Michel et al[31]	NS	NS	NS	NR
Sawitzke et al[39]	—	81.00	19.00	—
Uebelhart et al[40]	12.96	59.26	27.80	—
Glucosamine				
Reginster et al[36]	—	70.30	29.20	—
Pavelka et al[32]	—	55.40	44.60	—
Sawitzke et al[39]	—	80.50	19.50	—
Hyaluronic acid				
Wang et al[43]	—	75.60	24.40	—
Pham et al[34]	2.80	22.70	69.40	2.80
Listrat et al[24]	NS	NS	NS	NR
Vitamin D				
McAlindon et al[30]	—	50.00	28.80	21.20
Vitamin E				
Wluka et al[44]	26.50	39.70	30.10	—
NSAIDs				
Dieppe et al[10]	1.90	45.70	42.90	6.70
Buckland-Wright et al[6]	NS	NS	NS	NR
Pham et al[34]	2.90	18.20	74.10	2.90
Sawitzke et al[39]	—	72.60	27.40	—

[a]—, not applicable; NR, not reported; NSAID, nonsteroidal anti-inflammatory drug.

sulfate group in the Kahan et al,[19] Michel et al,[31] and Uebelhart et al[40] studies (Table 5). Sawitzke et al[39] did not note any significant difference in the narrowing of minimum JSW for those randomized to chondroitin sulfate (Table 5). Kahan et al[19] reported an odds ratio of experiencing OA progression with chondroitin sulfate of 0.45 (95% CI, 0.22-0.90), while Sawitzke et al[39] observed an odds ratio of 0.94 (95% CI, 0.57-1.55) (Table 5).

Kahan et al,[19] Michel et al,[31] and Sawitzke et al[39] reported no significant differences in pain reduction experienced between the chondroitin sulfate and placebo groups. Uebelhart et al[40] reported that those who received chondroitin sulfate experienced 42% less pain as measured by the VAS compared with 25% less in those who received placebo ($P = .05$).[40]

Effect of Glucosamine on JSW, OA Progression, and Pain

Three studies were identified that investigated the effects of glucosamine on structural variables for a mean duration of 32 months.[32,36,39] Baseline characteristics were similar among studies, as were withdrawal rates for both glucosamine and placebo groups. Patient populations represented those diagnosed with primary OA according to American College of Rheumatology criteria that was confirmed to not be secondary to any pre-existing condition.[2] Patients were evaluated for Kellgren-Lawrence grading before enrollment (Table 3). All trials received a 5 for a Jadad score of scientific quality and had no major identifiable sources of bias (Table 4). Reginster et al[36] and Pavelka et al[32] reported receiving industry support. Those prescribed glucosamine in the Sawitzke et al[39] trial received 500 mg of glucosamine hydrochlorate 3 times daily compared with 1500 mg glucosamine sulfate once daily in the Reginster et al[36] and Pavelka et al[32] trials. Progression of OA was defined as a decrease in JSW of 0.50 mm by Reginster et al[36] and Pavelka et al[32] and 0.48 mm by Sawitzke et al.[39]

Reginster et al[36] and Pavelka et al[32] reported significant chondroprotective properties of glucosamine compared with placebo (Table 6). Loss of mean JSW was found to be significantly decreased in patients receiving glucosamine compared with those receiving placebo by 0.38 mm (95% CI, 0.02-0.73; $P = .04$) and 0.23 mm (95% CI, 0.09-0.37; $P = .001$), respectively (Table 6).[32,36] Additionally, Reginster et al[36] noted a reduced loss of minimum JSW of 0.51 mm (95% CI, 0.20-0.83; $P = .002$) in the glucosamine group (Table 6). Sawitzke et al[39] did not note any significant difference in the narrowing of minimum JSW for those prescribed glucosamine (Table 6). The odds of experiencing OA progression with glucosamine were 0.41 (95% CI, 0.21-0.81) in the Reginster et al[36] trial, 0.32 (95% CI, 0.11-0.94) in the Pavelka et al[32] trial, and 0.79 (95% CI, 0.48-1.30) in the Sawitzke et al[39] trial (Table 6).

Reginster et al[36] reported a 24.3 point reduction in the total WOMAC score in the glucosamine group compared with 9.8 points in the placebo group ($P = .016$). Pavelka et al[32] observed a 0.7-point greater reduction in the WOMAC pain subscore using the Likert scale version in the glucosamine group compared with the placebo group ($P = .03$). Sawitzke et al[39] did not note any significant differences in pain reduction between groups.

Effect of Intra-articular Injections of Hyaluronic Acid on JSW, OA Progression, and Pain

We identified 3 studies that investigated structural changes in response to hyaluronic acid injections for a mean of 16 months.[24,34,43] Population characteristics were similar among the studies. All included participants were diagnosed with primary OA according to American College of Rheumatology criteria. Baseline Kellgren-Lawrence scores are summarized in Table 3. No study noted a significant difference in withdrawal rates between the placebo and intervention groups (Table 1). Formulations used are summarized in Table 1.

Alterations in joint structure were reported as changes in minimum JSW and annual percentage change of medial and lateral tibiofemoral cartilage volumes determined by the computerized calculation of MRI scans. Wang et al[43] observed that those receiving Hylan lost 2.60% (95% CI, 1.20-4.10; $P = .0001$) less tibiofemoral cartilage in the medial compartment and 2.80% (95% CI, 0.90-4.70; $P = .005$) less in the lateral compartment (Table 7). Listrat et al[24] and Pham et al[34] did not report any significant

TABLE 4
Analysis of Remaining Potential Sources of Bias[a]

Study	Jadad Score (+2 if Described as Randomized and Blinded)	Adequate Sequence Generation (Jadad ±1)	Allocation Concealment	Adequate Blinding (Jadad ±1)	Addressed Incomplete Outcome Data (Jadad ±1)	Free of Selective Reporting	Free of Other Bias	Industry Participation
Kahan et al[19]	5	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Michel et al[31]	5	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Sawitzke et al[39]	5	Yes	Yes	Yes	Yes	Yes	Yes	No
Uebelhart et al[40]	5	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Reginster et al[36]	5	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Pavelka et al[32]	5	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Wang et al[43]	2	Unclear	No	No	Yes	Yes	Yes	Yes
Pham et al[34]	4	Yes	Yes	Unclear	Yes	Yes	Yes	No
Listrat et al[24]	3	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes
McAlindon et al[30]	5	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Wluka et al[44]	4	Yes	Unclear	Unclear	Yes	Yes	Yes	No
Dieppe et al[10]	3	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes
Buckland-Wright et al[6]	3	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes

[a]Including sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and industry involvement.

TABLE 5
Structural Changes in Patients Treated With Chondroitin Versus Placebo[a]

	Change in Mean JSW, Medial Compartment		Change in Minimum JSW, Medial Compartment		
Study	Difference (95% CI), mm	*P* Value	Difference (95% CI), mm	*P* Value	OR for OA Progression With Chondroitin (95% CI)
Kahan et al[19]	—	—	0.24	<.0001	0.45 (0.22 to 0.90)
Michel et al[31]	0.14 (0.01 to 0.27)	.04	0.12 (0.00 to 0.24)	.05	—
Sawitzke et al[39]	—	—	0.06 (–0.017 to 0.29)	NS	0.94 (0.57 to 1.55)
Uebelhart et al[40]	0.28 (0.01 to 0.55)	.04	0.27 (0.004 to 0.55)	.047	—

[a]Measures include difference in joint space width (JSW) loss experienced between treatment groups and odds ratio (OR) of osteoarthritis (OA) progression with chondroitin. —, not applicable; CI, confidence interval; NS, no significance.

TABLE 6
Structural Changes in Patients Treated With Glucosamine Versus Placebo[a]

	Change in Mean JSW, Medial Compartment		Change in Minimum JSW, Medial Compartment		
Study	Difference (95% CI), mm	*P* Value	Difference (95% CI), mm	*P* Value	OR for OA Progression With Glucosamine (95% CI)
Reginster et al[36]	0.38 (0.02 to 0.73)	.038	0.51 (0.20 to 0.83)	.002	0.41 (0.21 to 0.81)
Pavelka et al[32]	0.23 (0.09 to 0.37)	.001	—	—	0.32 (0.11 to 0.94)
Sawitzke et al[39]	—	—	0.15 (–0.07 to 0.38)	NS	0.79 (0.48 to 1.30)

[a]Measures include difference in joint space width (JSW) loss experienced between treatment groups and odds ratio (OR) of osteoarthritis (OA) progression with glucosamine. —, not applicable; CI, confidence interval; NS, no significance.

differences in JSW lost between treatment groups (P = .39 and .82, respectively). Pham et al[34] reported the odds ratio of experiencing a 0.50-mm increase in minimum JSW while receiving NRD101 to be 0.88 (95% CI, 0.43-1.80) (Table 7).

Pham et al[34] and Listrat et al[24] did not observe any differences in pain experienced from baseline to completion in between groups (P = .96 and .13, respectively). Wang et al,[43] supported by industry, received a Jadad score of 2 and was determined to have an unclearly stated sequence generation, a lack of allocation concealment, and a single-blinded protocol. Listrat et al,[24] also industry supported, received a score of 3 because of unclearly stated sequence generation, allocation concealment, and blinding procedures. Pham et al[34] scored a 4 because of unclear blinding protocols (Table 4).

TABLE 7
Structural Changes in Patients Treated With Hyaluronic Acid Versus Placebo[a]

	Change in Minimum JSW, Medial Compartment		
Study	Difference, mm	*P* Value	OR for OA Progression With Hyaluronic Acid (95% CI)
Pham et al[34]	NR	.82	0.88 (0.43-1.80)
Listrat et al[24]	0.30	.39	—

	Annual Change in Medial Tibial Cartilage		Annual Change in Lateral Tibial Cartilage	
Study	Difference (95% CI), %	*P* Value	Difference (95% CI), %	*P* Value
Wang et al[43]	2.60 (1.20-4.10)	.0001	2.80 (0.90-4.70)	.005

[a]Measures include difference in joint space width (JSW) loss, difference in annual rate of change of cartilage volume lost, and odds ratio (OR) of osteoarthritis (OA) progression between treatment groups. —, not applicable; CI, confidence interval; NR, not reported.

TABLE 8
Structural Changes in Patients Treated With Vitamin D Versus Placebo[a]

	Change in Mean JSW, Medial Compartment		Change in Combined Tibiofemoral Cartilage Volume	
Study	Difference (95% CI), mm	*P* Value	Difference (95% CI), %	*P* Value
McAlindon et al[30]	–0.12 (–0.38 to 0.14)	.35	–0.05 (–1.91 to 1.82)	.96

[a]Measures include difference in joint space width (JSW) loss and change in tibiofemoral cartilage volume between groups. CI, confidence interval.

TABLE 9
Structural Changes in Patients Treated With Vitamin E Versus Placebo[a]

	Adjusted Difference in Medial Tibiofemoral Cartilage Volume, %		Adjusted Difference in Lateral Tibiofemoral Cartilage Volume, %	
Study	Difference (95% CI)	*P* Value	Difference (95% CI)	*P* Value
Wluka et al[44]	–0.40 (–5.00 to 4.10)	.86	–2.90 (–8.10 to 2.40)	.28

[a]Measures include difference in change of medial and lateral tibiofemoral cartilage volumes experienced between treatment groups. CI, confidence interval.

Effect of Vitamins D and E on JSW and Pain

One randomized controlled trial each was identified that investigated the effect for vitamin D and vitamin E on joint structure variables. Study characteristics and baseline characteristics are summarized in Tables 1 and 3. Included participants met American College of Rheumatology criteria for primary OA. McAlindon et al[30] concluded that there was no significant effect of vitamin D on joint structure in patients with OA (Table 8). Wluka et al[44] did not note any significant effects of vitamin E on medial ($P = .86$) or lateral ($P = .28$) tibiofemoral cartilage volumes compared with placebo (Table 9). In addition, no significant differences were noted in pain reduction versus placebo for either vitamin D or vitamin E ($P = .17$ and .22, respectively).[30,44] McAlindon et al[30] received a 5 on the Jadad scale and lacked any major identifiable sources of bias, while Wluka et al[44] scored a 4 and lacked a clearly stated allocation concealment (Table 4).

Effect of NSAIDs on JSW, OA Progression, and Pain

Four trials were identified that investigated the structure-modifying properties of the NSAIDs celecoxib, diacerein, and diclofenac in OA.[6,10,34,39] There were no reported differences in baseline characteristics, withdrawal rates, and Kellgren-Lawrence scores when reported between the intervention and placebo groups (Tables 1 and 3).

No study observed a significant structure-modifying effect of its particular intervention on knee JSW. Buckland-Wright et al[6] observed a mean JSW decrease of 0.32 mm less in the diclofenac group compared with placebo, but the result was not significant (Table 10). Pham et al[34] also noted no significant differences in JSW loss between the diacerein and placebo groups ($P = .82$). Sawitzke et al[39] reported a mean of 0.055-mm (95% CI, –0.17 to 0.28) less narrowing of minimum JSW in the celecoxib group versus placebo, but the result was not significant (Table 10). The odds ratio of experiencing a 0.48-mm

TABLE 10
Structural Changes in Patients Treated With NSAIDs Versus Placebo[a]

Study	Change in Mean JSW, Medial Compartment		Change in Minimum JSW, Medial Compartment		OR for OA Progression With NSAIDs (95% CI)
	Difference (95% CI), mm	*P* Value	Difference (95% CI), mm	*P* Value	
Dieppe et al[10]	—	—	—	—	1.38 (0.39 to 4.90)
Buckland-Wright et al[6]	0.32	NS	—	—	—
Pham et al[34]	—	—	NR	.82	0.92 (0.42 to 2.00)
Sawitzke et al[39]	—	—	0.055 (–0.17 to 0.28)	NS	0.87 (0.53 to 1.43)

[a]Measures include difference in joint space width (JSW) loss and odds ratio (OR) of osteoarthritis (OA) progression between treatment groups. —, not applicable; CI, confidence interval; NR, not reported; NS, no significance; NSAID, nonsteroidal anti-inflammatory drug.

decrease in minimum JSW with celecoxib was calculated to be 0.87 (95% CI, 0.53-1.43).[39] Dieppe et al[10] reported the odds of experiencing a decrease of 2 mm in JSW to be 1.38 (95% CI, 0.39-4.90) (Table 10). No differences in pain reduction were observed between the intervention and placebo groups in any trial.[6,10,34,39]

Dieppe et al[10] and Buckland-Wright,[5] both industry-supported studies, received a Jadad score of 3. Study methods did not clearly describe protocols for sequence generation, allocation concealment, or blinding protocols. Pham et al[34] scored a 4 because of unclear blinding procedures. Sawitzke et al[39] received a score of 5 and lacked major identifiable sources of bias (Table 4).

DISCUSSION

The results of our systematic review suggest that the long-term use of both glucosamine and chondroitin sulfate may have a small but significant effect on slowing disease progression in patients with knee OA. We were unable to conclude if there were similar effects experienced with treatment using intra-articular injections of hyaluronic acid. Oral vitamin D, vitamin E, and the NSAIDs investigated showed no effects on the progression of knee joint OA. This is the first systematic review that simultaneously reviewed the structural efficacy of the 12 nutraceuticals identified for ≥2 years using uniform criteria for analysis. Previous meta-analyses have been performed for both chondroitin and glucosamine.[15,23] Our study differs from them by simultaneously investigating additional treatment options that have not been previously reviewed for structural efficacy among randomized controlled trials for ≥2 years. Additionally, we drew our conclusions based on repeated trends among studies rather than from pooled data.

The main structural measures extracted in this review included changes in JSW assessed on plain radiographs and changes in tibiofemoral cartilage volume assessed by MRI. Both measures, in addition to the 0.5- and 0.48-mm threshold for radiographic progression, respectively, have been validated in the assessment of cartilage degeneration and OA progression.[3,5,6,45] Even differences in joint space narrowing as small as 0.38 mm have been associated with a lower rate of disease progression and better outcomes.[29]

Overall, there was a strong correlation between chondroitin sulfate use and reduced joint space narrowing. Kahan et al,[19] Michel et al,[31] and Uebelhart et al[40] administered 800 mg chondroitin sulfate once daily. All 3 were statistically powered to detect changes in JSW at 80% and noted a significant difference in structural measures. However, all 3 were noted to have received industry support. Sawitzke et al[39] administered 400 mg chondroitin sulfate 3 times daily and was limited by a statistical power of only 55%, possibly predisposing it to a greater chance of reporting a lack of effect. A previous meta-analysis conducted by Hochberg[15] supports our conclusions. The author observed a 0.13-mm (95% CI, 0.06-0.19; $P = .0002$) difference in narrowing between the chondroitin sulfate and placebo groups after 2 years.[15]

Treatment with glucosamine was also associated with decreased joint space narrowing and a reduction in pain in our systematic review. Both of the industry-supported trials, Reginster et al[36] and Pavelka et al,[32] had statistical powers of 80% and 90%, respectively, and administered glucosamine sulfate at 1500 mg once daily as the medication of choice. Both noted significant preservation of joint cartilage and a reduction in OA progression and pain.[32,36] Sawitzke et al[39] had only 55% power and prescribed glucosamine hydrochlorate 500 mg 3 times a day. They did not find a significant effect on JSW, OA progression, or pain. Evidence has suggested that the glucosamine hydrochlorate preparation used may not be as effective as the glucosamine sulfate formulation tested in the other 2 trials and that multiple doses of glucosamine are absorbed less efficiently than a single dose.[16,42] Low statistical power combined with potentially lower drug levels of a supposedly less effective glucosamine formulation may have contributed to the negative findings observed.

Our conclusions are supported by previous meta-analyses that found that glucosamine sulfate treatment preserved joint cartilage after use for more than 2 years.[23,35] Lee et al[23] noted that the odds of experiencing a 0.50-mm decrease in JSW was 0.361 (95% CI, 0.204-0.640) for glucosamine after 3 years.

Intra-articular hyaluronic acid injections showed variable efficacy in reducing cartilage loss after a minimum of 1 year of treatment. One difficulty that we faced in evaluating the evidence available was the difference in formulations used between studies. The concentration and molecular weight of hyaluronic acid in solution are 2 of the most important factors determining synovial fluid resistance to shear stress.[12] In OA, both the concentration and molecular weight of hyaluronic acid in the joint are reduced, leading to increased susceptibility to mechanical damage.[28] All 3 trials included varied in the molecular weight of hyaluronic acid used. Wang et al[43] used the largest molecular weight formulation, Hylan (6000 kDa), and noted the most significant effects of hyaluronic acid on joint cartilage. However, the trial suffered from low scientific quality (Table 4). Listrat et al[24] used a midweight formulation, Hyalgan, of 500 to 730 kDa. They did not note any significant differences in JSW or pain versus placebo at completion, but they did note significant structural differences measured by 2 scores of an overall assessment of chondropathy. It too suffered from low scientific quality (Table 4). The third trial, Pham et al,[34] used the lowest molecular weight formulation, NRD101 (1.9 kDa), and noted no improvements in any structural or pain measure compared with placebo. We concluded that there could potentially be some structural benefit with the yearlong treatment of high molecular weight formulations. However, a link with industry support and positive results, along with an overall lack of high-quality studies, made it difficult to draw definitive conclusions for treatment recommendations at this time.

Neither study that we identified for vitamin D or vitamin E showed any evidence of changes to joint structure or pain symptoms. For the most part, these results parallel those of similar published trials and reviews.[4,7,14] With the results of the trials identified, we cannot support the use of vitamins D or E as structure-modifying agents to prevent the risk of progression of OA.

The 3 NSAIDs administered in the trials included in this study were celecoxib, diclofenac, and diacerein. None of the agents showed any significant differences in joint structure compared with placebo groups in the studies evaluated.[6,10,34,39] It is important to point out that the current use of these medications is primarily for the symptom control of OA and joint pain.

Recently, the American Academy of Orthopaedic Surgeons published clinical practice guidelines, making recommendations for the treatment of symptomatic OA.[18] It stated that the evidence is strong to advocate against the use of oral glucosamine and chondroitin as well as intra-articular injections of hyaluronic acid.[18] These guidelines are based on results of both short- and long-term clinical studies evaluating pain and reported functional improvement compared with placebo.[18] In this review, we chose to focus primarily on structural changes and OA progression at longer time points. This allowed us to comment on the value of treatments as "chondroprotective" options rather than as acute symptom-modifying drugs. Our conclusions differed from those recommendations against the use of glucosamine and chondroitin. Additionally, our results suggest that those recommendations against the use of hyaluronic acid may be at the least premature.

In the past several years, there has been a vast increase in the number of drugs purported to have joint-protecting properties. We sought to clarify the evidence available in the literature to support or refute the use of these treatment agents for chondroprotection. Although many of these have sufficient short-term evidence evaluating their efficacy, they lack long-term level 1 evidence. Agents that we investigated that fell under this category included oral polyunsaturated fatty acids, S-adenosylmethionine, avocado and soybean unsaponifiable fractions, methylsulfonylmethane, vitamin C, and intra-articular injections of PRP. All have shown variable efficacy as structure-modifying drugs in short-term studies, cohort trials, animal studies, and in OA of the hip.[7-9,11,25] However, a lack of long-term randomized, placebo-controlled trials makes determining their ability as chondroprotective drugs problematic. This study identified no randomized controlled trial evaluating the effectiveness of any of these agents to prevent the risk of OA progression of the knee.

The major limitation of this study is that all of the positive results reported come from industry-supported trials. In general, studies funded by industry report positive proindustry results more frequently than those without affiliation.[1] Although all industry-associated trials for glucosamine and chondroitin were of high scientific quality and lacked major identifiable sources of bias, their findings should be framed within the context of possible industry-related bias. It has been suggested that an association with industry should result in a lower Jadad score. Because the Jadad score is a number used to assess bias based on protocol quality, we thought that industry association deserved a separate but equally important notation. Because our conclusions are based strongly on their results, they must be understood in the context of the potential for bias. However, our results reflect the best currently available literature on this topic.

This study was limited by several other factors. We were unable to identify any trials that met our inclusion criteria for 6 of our 12 identified treatments. For those that we did identify, data were mainly short term. Long-term investigations of these agents that are necessary to make more definitive conclusions to support their use were sparse. Additionally, dosages, formulations, treatment schedules, duration, and outcome measures varied between studies, making comparisons more difficult and susceptible to bias. This review did not provide any pooled statistical analysis. Lastly, this review may represent an incomplete list of potentially chondroprotective treatment options and only focused on OA of the knee.

In conclusion, this review supports the use of both oral glucosamine and chondroitin sulfate as structure-modifying, "chondroprotective" drugs in patients suffering from OA of the knee. Further long-term randomized controlled trials of the effect of intra-articular hyaluronic acid injections are necessary to properly evaluate their effectiveness in delaying the radiographic progression of OA. We did not find any evidence to support the structure-modifying properties of low molecular weight

hyaluronic acid, vitamin D, vitamin E, or the NSAIDs celecoxib, diacerein, and diclofenac. The other agents evaluated, polyunsaturated fatty acids, S-adenosylmethionine, avocado and soybean unsaponifiable fractions, methylsulfonylmethane, vitamin C, and intra-articular injections of PRP, had no evidence in the literature to support or refute their use for preventing OA progression. Those who are at risk for developing OA may benefit from the use of once-daily oral glucosamine sulfate at 1500 mg and chondroitin sulfate at 800 mg to prevent disease progression.

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