Rheumatol Int (2010) 30:357–363
DOI 10.1007/s00296-009-0969-5

ORIGINAL ARTICLE

Effect of glucosamine or chondroitin sulfate on the osteoarthritis progression: a meta-analysis

Young Ho Lee · Jin-Hyun Woo · Seong Jae Choi · Jong Dae Ji · Gwan Gyu Song

Received: 22 April 2009 / Accepted: 3 May 2009 / Published online: 21 June 2009

Abstract The aim of this study was to assess the structural efficacies of daily glucosamine sulfate and chondroitin sulfate in patients with knee osteoarthritis (OA). The authors surveyed randomized controlled studies that examined the effects of long-term daily glucosamine sulfate and chondroitin sulfate on joint space narrowing (JSN) in knee OA patients using the Medline and the Cochrane Controlled Trials Register, and by performing manual searches. Meta-analysis was performed using a fixed effect model because no between-study heterogeneity was evident. Six studies involving 1,502 cases were included in this meta-analysis, which consisted of two studies on glucosamine sulfate and four studies on chondroitin sulfate. Glucosamine sulfate did not show a significant effect versus controls on minimum JSN over the first year of treatment (SMD 0.078, 95% CI −0.116 to −0.273, $P = 0.429$). However, after 3 years of treatment, glucosamine sulfate revealed a small to moderate protective effect on minimum JSN (SMD 0.432, 95% CI 0.235–0.628, $P < 0.001$). The same was observed for chondroitin sulfate, which had a small but significant protective effect on minimum JSN after 2 years (SMD 0.261, 95% CI 0.131–0.392, $P < 0.001$). This meta-analysis of available data shows that glucosamine and chondroitin sulfate may delay radiological progression of OA of the knee after daily administration for over 2 or 3 years.

Y. H. Lee (✉) · J.-H. Woo · S. J. Choi · J. D. Ji · G. G. Song
Division of Rheumatology, Department of Internal Medicine,
Korea University Anam Hospital,
Korea University College of Medicine, 126-1 ga,
Anam-dong, Seongbuk-gu, Seoul 136-705, Korea
e-mail: lyhcgh@korea.ac.kr

Keywords Glucosamine · Chondroitin · Knee · Osteoarthritis · Structural efficacy

Introduction

Osteoarthritis (OA) is the most common form of arthritis and is a leading cause of morbidity and disability [1]. Treatment strategies for OA include both non-pharmacological and pharmacological therapies. Drugs for OA treatment have been classified as symptom-modifying drugs or as structure-modifying drugs. Structure-modifying drugs should be able to favorably alter joint structure, and thus, affect disease progression [2].

Glucosamine is a normal constituent of glycosaminoglycans in cartilage matrix and synovial fluid, and glucosamine sulfate stimulates cultured human chondrocytes to synthesize proteoglycans, inhibits the actions of catabolic enzymes, and reduces IL-1β levels in synovial fluid [3, 4]. On the other hand, chondroitin sulfate is a major component of the extracellular matrix of connective tissues [5]. Furthermore, in articular cartilage, high levels of chondroitin sulfate in aggrecan plays a major role in creating considerable osmotic pressure that expands the matrix and places the collagen network under tension [6].

The therapeutic effects of glucosamine and chondroitin sulfate in OA have been studied for 20 years, and their symptom relieving efficacies were recently analyzed by high-quality meta-analysis [7, 8]. Moreover, both have been used as safe and effective options for the management of the symptoms of OA [9, 10]. However, the ultimate goal of OA treatment is to prevent or at least retard disease progression. For structure-modifying agents, prospective evaluations of radiographic joint space narrowing (JSN) changes are required. Previous several studies have

demonstrated by JSN analysis the possibility that glucosamine sulfate and chondroitin sulfate modify the disease state, but their effects remain debatable [11–16].

Meta-analysis is a statistical procedure that allows the results of several studies to be combined to produce overall estimates of major effects with enhanced precision [17]. The major advantage of meta-analysis is that increases sample size, which possibly reduces the likelihood that random errors will produce false-positive or false-negative associations.

We performed meta-analysis on the data produced by available randomized controlled trials (RCTs) on the disease-modifying effects of glucosamine and chondroitin sulfate in OA of the knee. Thus, the aim of the present study was to investigate the structural efficacies of glucosamine sulfate and chondroitin sulfate in patients with OA of the knee, using a meta-analysis approach.

Methods

Identification of eligible studies and data extraction

We performed an exhaustive search for studies that examined the effects of glucosamine sulfate and chondroitin sulfate on knee JSN in OA patients. Literature searches were performed using MEDLINE and the Cochrane Controlled Trials Register to identify available articles (the most recent article was published in July 2008). The following key words and subject terms were used in the searches: 'glucosamine', 'chondroitin', 'knee', 'cartilage', 'structure' and 'osteoarthritis.' In addition, all cited references were reviewed to identify additional works, which are not indexed by electronic databases. Results were limited to English language papers. All randomized controlled studies that compared glucosamine sulfate or chondroitin sulfate with a placebo in patients with OA were considered eligible if they utilized JSN as an outcome variable after treatment commencement. Studies were excluded if they did not contain a placebo group, the OA site was not the knee joint, they did not contain adequate data, and when the study concerned was cross-sectional. We quantified the methodological qualities of primary studies using Jadad scores [18].

The following information was extracted from each study: first author, year of publication, dose of glucosamine or chondroitin, length of follow-up, intention to treat analysis, mean and SD of JSN (change-from-baseline), and number of patients who experienced a clinically relevant (>0.5 mm) mean JSN. When no SD data was provided, we imputed SD values from 95% confidence intervals (CI). SDs were calculated by dividing the length of the confidence interval by 3.92 and then multiplying the result by the square root of the sample size.

Evaluation of publication bias

Funnel plots were used to detect publication bias. However, because funnel plots require a range of studies of different sizes and subjective judgments, we evaluated publication bias using Egger's linear regression test [19]. Egger's test measures funnel plot asymmetry using a natural logarithm scale of odds ratios (ORs).

Evaluation of statistical associations

Standardized mean differences (SMDs) were used for JSN analysis and ORs were used to analyze severe narrowing (>0.5 mm). SMDs were calculated by dividing the difference between the glucosamine or chondroitin and control groups by baseline variance. This measure compares treatment and placebo arms in terms of standardized scores. A treatment that is one unit better than the placebo is 1 SD better, based on variations in original JSNs. An SMD scale for effect sizes was suggested by Cohen, where 0.8 reflects a large effect, 0.5 a moderate effect, and 0.2 a small effect [20].

We assessed within- and between-study variations and heterogeneities using Cochran's Q-statistics. The heterogeneity test was used to assess the null hypothesis that all studies evaluated the same effect. If the significant Q-statistic ($P < 0.10$) indicates heterogeneity across studies then the random effects model should be used for meta-analysis. This model assumes that different studies may estimate different underlying effects, and considers both intra- and inter-study variations [21]. In the present study, we used the fixed effects model because heterogeneity was not identified.

We quantified the effect of heterogeneity using $I^2 = 100\% \; x \; (Q\text{-}df)/Q$, where I^2 measures the degree of inconsistency between studies and determines whether the percentage total variation across studies is due to heterogeneity rather than chance [22]. I^2 ranges between 0 and 100%; I^2 values of 25, 50, and 75% are referred to as low, moderate, and high estimates.

We also performed sensitivity analyses by limiting studies based on short ≤1 years) or long (≥2 years) follow-up periods. Statistical manipulations were undertaken using a Comprehensive Meta-Analysis computer program (Biosta, Englewood, NJ, USA).

Results

Studies included in the meta-analysis

Two hundred and ninety-three studies were identified by electronic or manual search and nine were selected for

full-text review based on title/abstract details. However, 3 of the 11 studies were excluded; one for OA of hip [23] and two studies because they were not written in English [24, 25]. Thus, six studies met the inclusion criteria [11–16]. These 6 studies involved a total of 749 patients and 753 controls, and 2 glucosamine and 4 chondroitin trials that reported information on JSN assessments. The characteristic features of the studies included in the meta-analysis are given in Table 1. Individual demographic baselines were well matched between studies. Follow-up periods ranged from 1 to 3 years and quality scores ranged from 3 to 5. Five of the six studies were ITT analysis.

Meta-analysis of the effect of glucosamine sulfate on knee JSN

Two studies of glucosamine sulfate analyzed knee JSN [11, 12]. We examined the effect sizes 1 and 3 years after glucosamine sulfate treatment commencement, respectively. Glucosamine sulfate showed no significant effect versus controls on minimum JSN after 1 year of treatment (SMD 0.078, 95% CI −0.116 to −0.273, $P = 0.429$) (Table 2; Fig. 1). However, at 3 years, glucosamine sulfate revealed a small to moderate protective effect on minimum JSN (SMD 0.432, 95% CI 0.235–0.628, $P < 0.001$) (Table 2; Fig. 1). Meta-analysis based on severe JSN criteria showed that glucosamine sulfate had a protective effect versus controls (OR 0.361, 95% CI 0.204–0.640, $P < 0.001$) (Table 2; Fig. 1).

Meta-analysis of the effect of chondroitin sulfate on knee JSN

Four studies analyzed knee JSN [13–16]. After 2 years on chondroitin sulfate, a small protective effect was observed versus controls on both minimum and mean JSNs (SMD 0.317, 95% CI 0.136–0.497, $P = 0.001$, SMD 0.236, 95% CI 0.148–0.386, $P < 0.001$) (Table 2; Fig. 2). We divided studies according to follow-up period. Chondroitin sulfate showed no significant effect versus controls on minimum JSN after 1 year of treatment (SMD 0.295, 95% CI 0.000–0.590, $P = 0.050$) (Table 2; Fig. 3). However, at 2 years, chondroitin sulfate revealed a small but significant protective effect on minimum JSN (SMD 0.261, 95% CI 0.131–0.392, $P < 0.001$) (Table 2; Fig. 3).

Heterogeneity and publication bias

No between-study heterogeneity was found during any analysis, and thus, all meta-analyses were performed using a fixed-effect model. It was difficult to correlate the funnel plot, which is usually used to detect publication bias, because the number of studies included was too small.

Table 1 Characteristics of individual studies included in meta-analysis

Study	Dose	Age*		Sex (%)		BMI (kg/m^2)		Drop rate (%)		Numbers		Follow-up period (years)	Variables analyzed	ITT analysis	Quality score
		OA	C	OA	C	OA	C	OA	C	OA	C				
Pavelka et al. [11]	GS 1,500 mg once a day	61.2 (7.3)	63.5 (6.9)	80 (79)	77 (76)	25.7 (2.1)	25.7 (1.8)	34.6	45.5	101	101	3	Minimum JSN Severe narrowing	Yes	5
Reginster et al. [12]	GS 1,500 mg once a day	66.0 (8.1)	65.5 (7.5)	79 (75)	83 (78)	27.3 (2.6)	27.4 (2.7)	33.0	35.8	106	106	3	Minimum JSN, Mean JSN Severe narrowing	Yes	5
Kahan et al. [13]	CS 800 mg once a day	NA	NA	68	68	NA	NA	30.1	25.6	309	313	2	Mean JSN	Yes	NA
Michel et al. [14]	CS 800 mg once a day	62.5 (9.1)	63.1 (10.7)	76 (51)	78 (52)	27.7 (5.2)	28.1 (5.5)	26.6	27.3	150	150	2	Minimum JSN, Mean JSN	Yes	5
Uebelhart-1 et al. [15]	CS 800 mg 2 periods of 3 months during 1 year	63.2 (9.1)	63.7 (8.1)	79.6	82.1	NA	NA	28.3	31.6	60	60	1	Minimum JSN, Mean JSN	Yes	3
Uebelhart-2 et al. [16]	CS 400 × 2 mg a day	6013	5711	47.8	56.5	NA	NA	8.7	8.7	23	23	1	Minimum JSN, Mean JSN	No	3

OA Osteoarthritis, *C* control, *ITT* intention-to-treat, *GS* glucosamine sulfate, *CS* chondroitin sulfate, *NA* not available, *JSN* joint space narrowing

[a] Mean (SD)

Table 2 Meta-analysis of the structural effect of glucosamine and chondroitin sulfate on cartilage in knee OA

Drug	Group	No. of Studies	Test of association			Test of heterogeneity			
			Std diff in means	95% CI	*P* values	Model	Q	*P* values	I^2
Glucosamine sulfate	Follow-up for 1 years	2	0.078	−0.116–0.273	0.429	F	1.14	0.284	12.7
	Follow-up for 3 years	2	0.432	0.235–0.628	0.000	F	0.03	0.848	0
	JSN > 0.5 mm	2	0.361[a]	0.204–0.640	0.000	F	0.05	0.810	0
Chondroitin sulfate	Minimum JSW	3	0.317	0.136–0.497	0.001	F	2.14	0.342	6.9
	Mean JSW	4	0.236	0.148–0.386	0.000	F	0.07	0.995	0
	Follow-up for 1 year	2	0.295	0.000–0.590	0.050	F	0.00	0.965	0
	Follow-up for 2 years	2	0.261	0.131–0.392	0.000	F	0.02	0.864	0

F fixed effect model, *R* random effect model, *JSW* joint space width, *JSN* joint space narrowing

[a] Odds ratio

However, no indication of publication bias was evident (Egger's regression test *P* values > 0.1).

Discussion

Published evidence supports the efficacies of glucosamine sulfate and chondroitin sulfate in terms of delaying structural progression in knee OA. With respect to the structure-modifying effects of treatment, this meta-analysis provides evidence that both glucosamine sulfate and chondroitin sulfate inhibit the progression of knee OA. In this meta-analysis, structural efficacies were estimated using JSN and number of severe narrowings as measures of efficacy. Joint structural changes were assessed on radiographs and are represented by joint

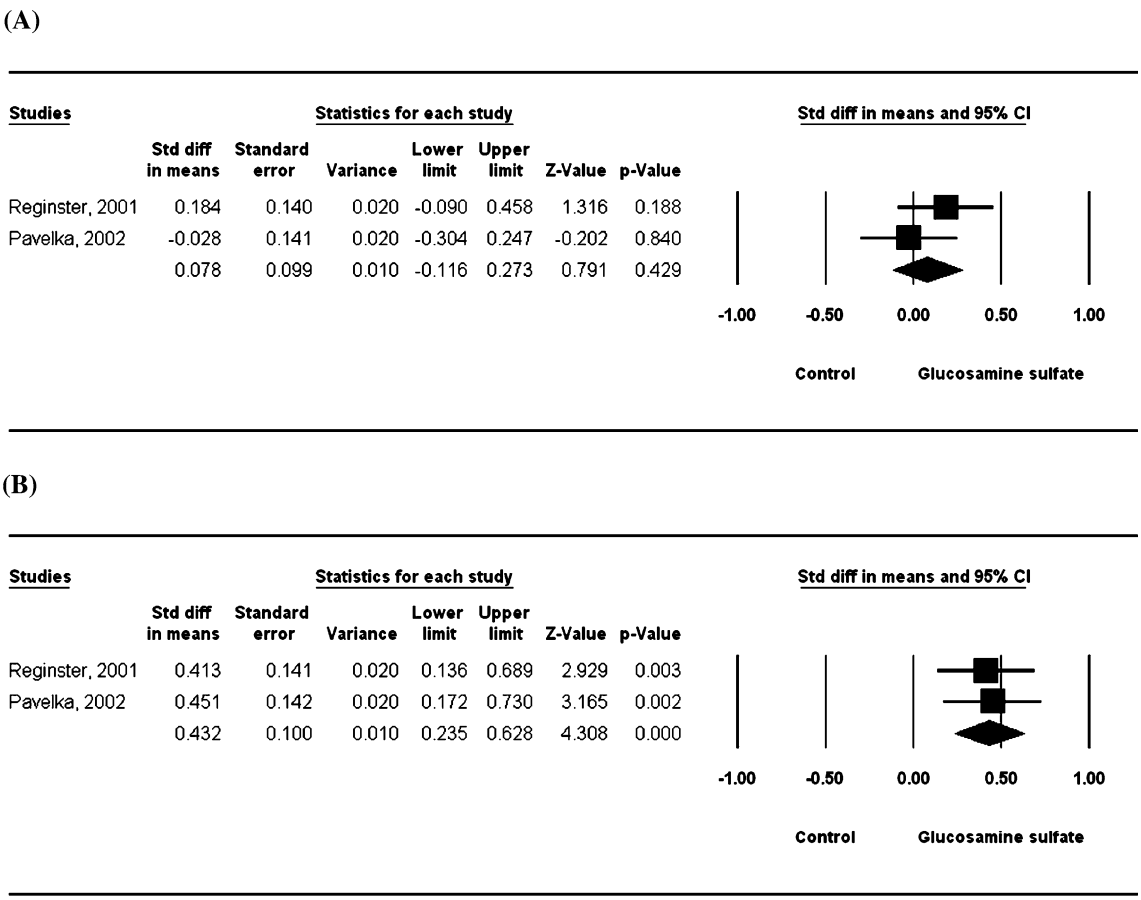
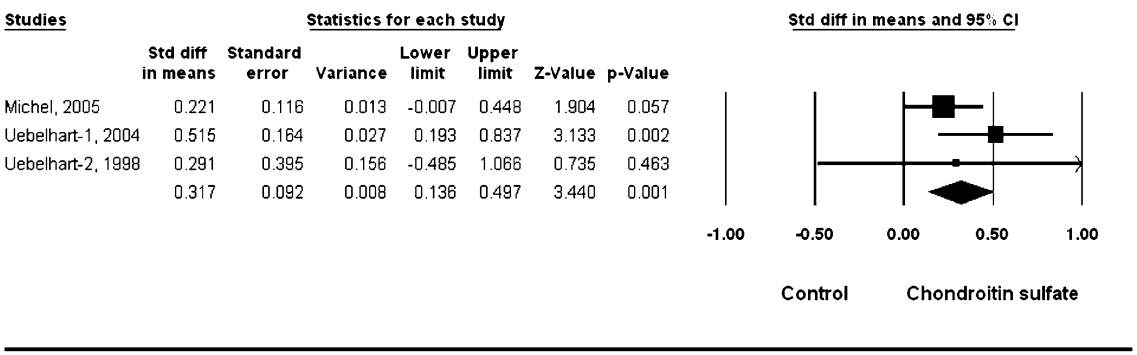


Fig. 1 Standard difference in the mean values and 95% CI of individual studies and pooled data for the structural effect of glucosamine sulfate on minimum JSN in knee OA after 1 year (**a**) and 3 years (**b**) of treatment

(A)



(B)

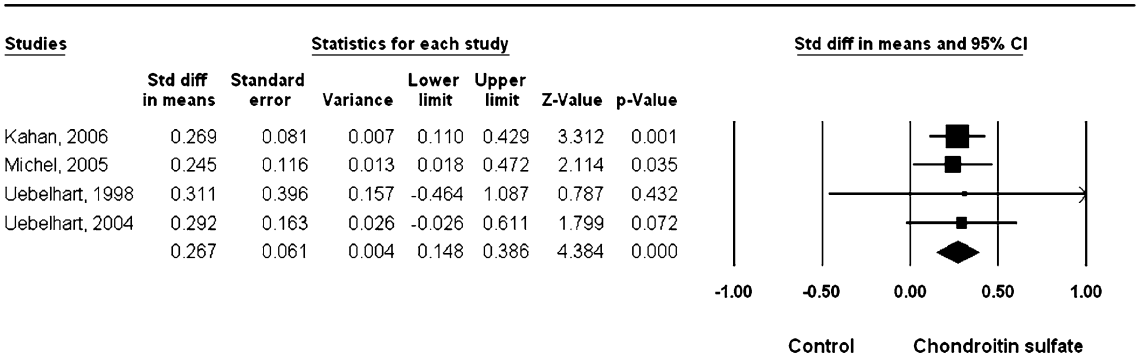


Fig. 2 Standard difference in the mean values and 95% CIs of individual studies and pooled data of the structural effects of glucosamine sulfate on minimum (**a**) and mean JSNs (**b**) in knee OA

space width changes for individual studies. Furthermore, joint structural damage progression was arbitrarily defined as a JSN of >0.5 mm, because the 0.5 mm cutoff was suggested to be clinically relevant in a study that investigated the efficacies of disease-modifying drugs in OA [26].

Glucosamine sulfate did not show a significant effect versus controls on minimum JSN after 1 year of treatment,

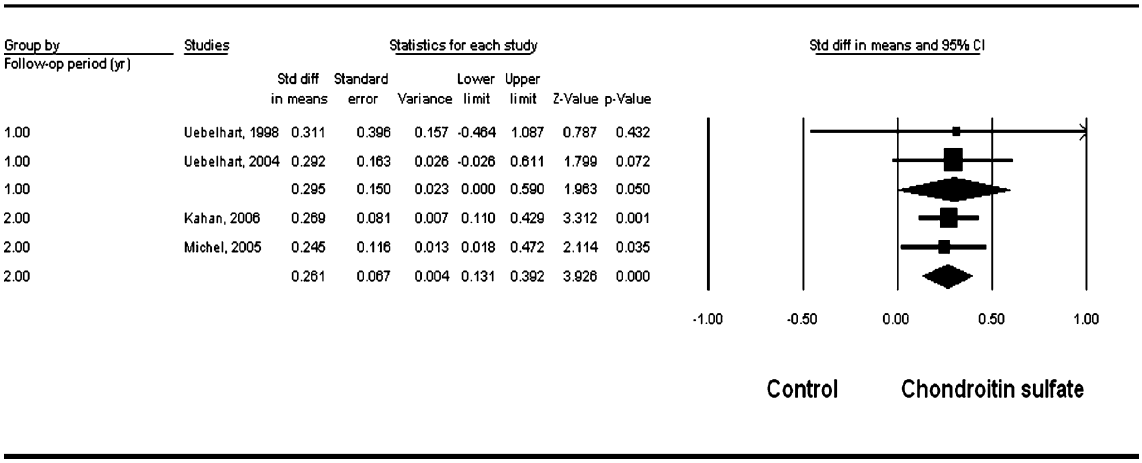


Fig. 3 Standard difference in the mean values and 95% CIs of individual studies and pooled data for the structural effects of chondroitin sulfate on mean JSN in knee OA at 1 and 2 years after treatment commencement

but glucosamine sulfate revealed a small to moderate chondroprotective effect after 3 years. Furthermore, the percentage of patients who experienced a clinically relevant (>0.5 mm) mean JSN after 3 years was significantly lower in the glucosamine sulfate group than in the control group. The same protective pattern was observed for chondroitin sulfate by meta-analysis over 1 and 2 years, and chondroitin sulfate revealed a small but significant protective effect on minimum JSN after 2 years of treatment. This meta-analysis indicates that the minimum duration of clinical trials to establish a disease-modifying effect is 2 years. It is also important to note that the sulfate salt of glucosamine (a prescription medicine produced by the Rotta Pharmaceutical Company, Italy) was used in two studies included in this glucosamine meta-analysis. Glucosamime sulfate is approved as a prescription drug for OA in the European Union, and glucosamine (considered a nutritional supplement in North America and Asia) is available in a sulfate or hydrochloride form. However, it has not been established whether different forms of glucosamine have different chondroprotective effects. A previous meta-analysis of glucosamine on OA symptoms concluded that while glucosamine sulfate is effective, glucosamine hydrochloride is not [7]. Subgroup analyses of the Rotta preparation showed significant benefit over placebo in terms of pain and Lequesne index [27]. For non-Rotta preparations, pooled results showed no statistically significant difference in pain. Thus, the structural efficacies of other forms of glucosamine cannot be predicted. The results of our meta-analysis should be treated with caution.

Our analysis differed from previous meta-analyses in terms of the structural efficacies of glucosamine sulfate and chondroitin sulfate in OA. Three meta-analyses of glucosamine sulfate used end of study data and performed analysis over a 3-year period [28]. In contrast, we performed this meta-analysis using the change-from-baseline data over 1 and 3 years. The chondroitin meta-analysis by Reichenbach et al. [8] also used end-of-period data, whereas in the present study, this data were also analyzed using change-from-baseline data at 1 and 2 years. Different sets of studies were used in the chondroitin meta-analysis and our study. Reichenbach et al. [8] included Conrozier's and Malaise et al.'s studies [24, 25], but we excluded these studies because they were not reported in English. However, results were similar in both studies.

The present study has some shortcomings that should be considered. First, available data suggest that glucosamine sulfate and chondroitin sulfate may be effective disease-modifying OA drugs, but data on the long-term use of glucosamine sulfate and chondroitin sulfate on structure changes in knee OA are sparse. Furthermore, because of the relatively sparse data on glucosamine sulfate and chondroitin sulfate and JSN, further studies on their structural effects are needed. Second, the results of this meta-analysis were obtained using prescription drugs containing glucosamine sulfate 1,500 mg produced by the Rotta Pharmaceutical Company. Since the content and purity of the various over-the-counter preparations available are known to vary markedly, the relative efficacies of the various preparations may also vary. Moreover, this result should not be extrapolated to over-the-counter preparations or food supplements, as their contents and pharmacokinetics cannot be guaranteed. Third, in addition to glucosamine formulations, dosages may affect the efficacy of glucosamine sulfate. The apparent superior profile of the Rottapharm product might also due to its unique once-per-day formulation. Furthermore, the possibility of a dosage effect could not be evaluated due to limited data. Fourth, this study was limited to knee OA, and thus, out findings cannot be extrapolated to other OA sites, such as, the hip and interphalangeal joints.

In conclusion, this meta-analysis suggests that glucosamine sulfate and chondroitin sulfate may delay the natural radiological progression of OA of the knee. The long-term administration of daily oral glucosamine sulfate at 1,500 mg over a minimal period of 3 years or daily oral chondroitin sulfate at 800 mg over a minimal period of 2 years may retard degenerative processes affecting knee joint cartilage.

References

1. Creamer P, Hochberg MC (1997) Osteoarthritis. Lancet 350:503–508
2. Verbruggen G (2006) Chondroprotective drugs in degenerative joint diseases. Rheumatology 45:129–138
3. Reginster JY, Bruyere O, Neuprez A (2007) Current role of glucosamine in the treatment of osteoarthritis. Rheumatology 46:731–735
4. Largo R, Alvarez-Soria MA, Diez-Ortego I, Calvo E, Sanchez-Pernaute O, Egido J, Herrero-Beaumont G (2003) Glucosamine inhibits IL-1beta-induced NFkappaB activation in human osteoarthritic chondrocytes. Osteoarthr Cartil 11:290–298
5. Hardingham T (1998) Chondroitin sulfate and joint disease. Osteoarthr Cartil 6(Suppl A):3–5
6. Bali JP, Cousse H, Neuzil E (2001) Biochemical basis of the pharmacologic action of chondroitin sulfates on the osteoarticular system. Semin Arthritis Rheum 31:58–68
7. Vlad SC, LaValley MP, McAlindon TE, Felson DT (2007) Glucosamine for pain in osteoarthritis: why do trial results differ? Arthritis Rheum 56:2267–2277
8. Reichenbach S, Sterchi R, Scherer M, Trelle S, Burgi E, Burgi U, Dieppe PA, Juni P (2007) Meta-analysis: chondroitin for osteoarthritis of the knee or hip. Ann Intern Med 146:580–590
9. Jordan KM, Arden NK, Doherty M, Bannwarth B, Bijlsma JW, Dieppe P, Gunther K, Hauselmann H, Herrero-Beaumont G, Kaklamanis P, Lohmander S, Leeb B, Lequesne M, Mazieres B, Martin-Mola E, Pavelka K, Pendleton A, Punzi L, Serni U, Swoboda B, Verbruggen G, Zimmerman-Gorska I, Dougados M (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 (ESCISIT). Ann Rheum Dis 62:1145–1155
10. Zhang W, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N, Bierma-Zeinstra S, Brandt KD, Croft P, Doherty M, Dougados M, Hochberg M, Hunter DJ, Kwoh K, Lohmander LS, Tugwell P (2008) OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. Osteoarthr Cartil 16:137–162
11. Pavelka K, Gatterova J, Olejarova M, Machacek S, Giacovelli G, Rovati LC (2002) Glucosamine sulfate use and delay of progression of knee osteoarthritis: a 3-year, randomized, placebo-controlled, double-blind study. Arch Intern Med 162:2113–2123
12. Reginster JY, Deroisy R, Rovati LC, Lee RL, Lejeune E, Bruyere O, Giacovelli G, Henrotin Y, Dacre JE, Gossett C (2001) Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomised, placebo-controlled clinical trial. Lancet 357:251–256
13. Kahan A, Reginster JY, Vignon E. STOPP (Study on Osteoarthritis Progression Prevention): a new two-year trial with chondroitin 4&6 sulfate (CS) [abstract]. EULAR 2006 June 23; Amsterdam, The Netherlands: Institut Biochimique SA (IBSA). Available at http://www.ibsa-ch.com/welcome-head/rd-symposia-past_events-2006-intl.htm?id=1439
14. Michel BA, Stucki G, Frey D, De Vathaire F, Vignon E, Bruehlmann P, Uebelhart D (2005) Chondroitins 4 and 6 sulfate in osteoarthritis of the knee: a randomized, controlled trial. Arthritis Rheum 52:779–786
15. Uebelhart D, Malaise M, Marcolongo R, de Vathaire F, Piperno M, Mailleux E, Fioravanti A, Matoso L, Vignon E (2004) Intermittent treatment of knee osteoarthritis with oral chondroitin sulfate: a one-year, randomized, double-blind, multicenter study versus placebo. Osteoarthritis Cartilage 12:269–276
16. Uebelhart D, Thonar EJ, Delmas PD, Chantraine A, Vignon E (1998) Effects of oral chondroitin sulfate on the progression of knee osteoarthritis: a pilot study. Osteoarthr Cartil 6(Suppl A):39–46
17. Egger M, Smith GD, Phillips AN (1997) Meta-analysis: principles and procedures. BMJ 315:1533–1537
18. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ (1996) Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 17:1–12
19. Egger M, Davey Smith G, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. BMJ 315:629–634
20. Corbett J, Gu CC, Rice JP, Reich T, Province MA, Rao DC (2004) Power loss for linkage analysis due to the dichotomization of trichotomous phenotypes. Hum Hered 57:21–27
21. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials 7:177–188
22. Higgins JP, Thompson SG (2002) Quantifying heterogeneity in a meta-analysis. Stat Med 21:1539–1558
23. Rozendaal RM, Koes BW, van Osch GJ, Uitterlinden EJ, Garling EH, Willemsen SP, Ginai AZ, Verhaar JA, Weinans H, Bierma-Zeinstra SM (2008) Effect of glucosamine sulfate on hip osteoarthritis: a randomized trial. Ann Intern Med 148:268–277
24. Conrozier T (1998) Anti-arthrosis treatments: efficacy and tolerance of chondroitin sulfates (CS 4&6). Presse Med 27:1862–1865 (French)
25. Malaise M, Marcolongo R, Ubelhart D, Vignon E (1999) Efficacy and tolerability of 800 mg oral chondroitin 4&6 sulfate in the treatment of knee osteoarthritis: a randomized, double-blind, multicentre study versus placebo. Lit Rheumatol 24:31–42 (German)
26. Ravaud P, Giraudeau B, Auleley GR, Drape JL, Rousselin B, Paolozzi L, Chastang C, Dougados M (1998) Variability in knee radiographing: implication for definition of radiological progression in medial knee osteoarthritis. Ann Rheum Dis 57:624–629
27. Towheed TE, Anastassiades T (2007) Glucosamine therapy for osteoarthritis: an update. J Rheumatol 34:1787–1790
28. Richy F, Bruyere O, Ethgen O, Cucherat M, Henrotin Y, Reginster JY (2003) Structural and symptomatic efficacy of glucosamine and chondroitin in knee osteoarthritis: a comprehensive meta-analysis. Arch Intern Med 163:1514–1522