



Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas



Review

What is the current status of chondroitin sulfate and glucosamine for the treatment of knee osteoarthritis?

Yves Henrotin^{a,*}, Marc Marty^b, Ali Mobasheri^{c,d,e}

^a Bone and Cartilage Research Unit, Arthropôle Liège, University of Liège, Institute of Pathology, CHU Sart-Tilman, 4000 Liège, Belgium

^b Rheumatology Department, Teaching Hospital H Mondor, Creteil, France

^c School of Veterinary Medicine, Faculty of Health and Medical Sciences, University of Surrey, Duke of Kent Building, Guildford, Surrey GU2 7XH, United Kingdom

^d Arthritis Research UK Centre for Sport, Exercise and Osteoarthritis, Arthritis Research UK Pain Centre, Medical Research Council and Arthritis Research UK Centre for Musculoskeletal Ageing Research, University of Nottingham, Queen's Medical Centre, Nottingham, NG7 2UH, United Kingdom

^e Center of Excellence in Genomic Medicine Research (CEGMR), King Fahd Medical Research Center (KFMRC), King AbdulAziz University, Jeddah, 21589, Kingdom of Saudi Arabia

ARTICLE INFO

Article history:

Received 8 April 2014

Accepted 12 April 2014

Available online xxx

Keywords:

Chondroitin
Glucosamine
Osteoarthritis
Cartilage

ABSTRACT

Chondroitin sulfate and glucosamine sulfate exert beneficial effects on the metabolism of *in vitro* models of cells derived from synovial joints: chondrocytes, synoviocytes and cells from subchondral bone, all of which are involved in osteoarthritis (OA). They increase type II collagen and proteoglycan synthesis in human articular chondrocytes and are able to reduce the production of some pro-inflammatory mediators and proteases, to reduce the cellular death process, and improve the anabolic/catabolic balance of the extracellular cartilage matrix (ECM). Clinical trials have reported a beneficial effect of chondroitin sulfate and glucosamine sulfate on pain and function. The structure-modifying effects of these compounds have been reported and analyzed in recent meta-analyses. The results for knee OA demonstrate a small but significant reduction in the rate of joint space narrowing. Chondroitin sulfate and glucosamine sulphate are recommended by several guidelines from international societies for the management of knee and hip OA, while others do not recommend these products or recommend only under condition. This comprehensive review clarifies the role of these compounds in the therapeutic arsenal for patients with knee OA.

© 2014 The Authors. Published by Elsevier Ireland Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/3.0/>).

Contents

1. Introduction	00
2. Methods	00
2.1. CS and GlcN in clinical trials	00
2.1.1. Glucosamine (GlcN)	00
2.1.2. Chondroitin sulfate (CS)	00
2.1.3. GlcN and CS in combination	00
2.2. GINc and CS in guidelines	00
3. Discussion and conclusions	00
Contributors	00
Competing interest	00
Funding	00
Provenance and peer review	00
References	00

* Corresponding author at: Bone and Cartilage Research Unit (BCRU), University of Liège, CHU Sart-Tilman, Institute of Pathology, Level +5, Sart-Tilman, 4000 Liège, Belgium. Tel.: +32 43662516.

E-mail address: yhenrotin@ulg.ac.be (Y. Henrotin).

<http://dx.doi.org/10.1016/j.maturitas.2014.04.015>

0378-5122/© 2014 The Authors. Published by Elsevier Ireland Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/3.0/>).

Please cite this article in press as: Henrotin Y, et al. What is the current status of chondroitin sulfate and glucosamine for the treatment of knee osteoarthritis? Maturitas (2014), <http://dx.doi.org/10.1016/j.maturitas.2014.04.015>

1. Introduction

Osteoarthritis (OA), one of the most disabling arthritic conditions, is now clearly defined as a disease of the whole organ; namely, the synovial joint [1]. It is acknowledged that cartilage is not the sole tissue affected by OA, but that the subchondral bone and the synovial membrane (SM) undergo metabolic and structural modifications as the disease progresses [2].

The complexity of OA pathogenesis is a matter of fact and its management represents a challenge for the scientific community. Recently, different OA phenotypes have been described including obesity-related OA, mechanical-induced OA and aging-related OA. This suggests that OA treatment could be stratified and tailored to the relevant phenotype [3]. A key challenge will be to identify phenotypes for particular treatments. Until now, the management of OA has consists mostly of symptom management, i.e. reduction of pain and improvement of joint function, which relies on the combination of non-pharmacologic and pharmacologic approaches as has been proposed by the main published guidelines [4–10]. Although important, the control of symptoms is not the only goal that needs to be achieved in OA patients. Indeed the ideal treatment for OA should preserve the joint structures, keeping in mind the improvement in the quality of life of patients [11] and exhibit a good safety profile. It is paramount to take into account the side effect due to the chronic use of OA therapies, such as NSAIDs [12].

Glycosaminoglycans such as chondroitin sulfate (CS) and glucosamine (GlcN) are two natural compounds considered as Symptomatic Slow Acting Drugs for Osteoarthritis (SYSADOA). Moreover, some of these compounds were also demonstrated to possess disease-modifying (DMOAD) potential based on the measurement of joint space narrowing on radiographs. Nevertheless, the use of these products as well as the relevance of their clinical efficacy are constantly under debate since they could be sold “over the counter” as dietary supplements in North America whereas they are registered drugs in Europe. This narrative review will provide an update on the potential mechanisms of action of CS and GS and the results of clinical trials will be further documented and discussed.

2. Methods

The literature search was performed using the PubMed/Medline databases between January 2009 and January 2014. Searches were performed in PubMed using the search terms “glucosamine”, “chondroitin sulphate”, “pharmaceutical-grade”, “osteoarthritis”, “randomized clinical trials”, “humans”. The MEDLINE database was searched for all randomized controlled trials, meta-analyses (MAs), systematic reviews, and review articles of chondroitin sulfate and glucosamine sulphate in OA.

Only articles published in English were included and clinical studies including knee OA patients were considered. Studies on the therapeutic effects of injectable substances were excluded.

2.1. CS and GlcN in clinical trials

In the following sections we review the evidence for CS and GlcN in published clinical trials.

2.1.1. Glucosamine (GlcN)

The DMOAD effect of GlcN was analyzed in recent MAs [13,14]. Wandel et al. reported no relevant clinical effect based on an effect size (ES) on joint pain of -0.17 (-0.28 to -0.05) and on joint space width (JSW) of -0.16 (-0.25 to 0.00) [13]. However, this MA showed numerous limitations and the interpretation of the data was hazardous with regards to the data [15]. Several expert groups in the field of OA have questioned the validity of the conclusions. Pitfalls of this MA were addressed in part in the report from the

British Medical Journal post-publication review meeting, which states that the data of the study did not directly support the strong negative conclusion of the study (Groves T. Report from BMJ post publication review meeting. Available at: http://www.bmj.com/content/341/bmj.c4675.full%20./reply#bmj_el.247719 [accessed 19.06.11]).

The other MA, including only two trials [14], reported a small to moderate protective effect of GlcN-S on the minimum JSN after 3 years in knee OA. This was in accordance with the data of a recent trial indicating that GlcN-S prevented total knee replacement (TKR) [16]. In contrast, no effect was observed in hip OA with GlcN-S [17]. It is noteworthy that the Glucosamine/chondroitin Arthritis Trial (GAIT) study, the largest randomized controlled trial (RCT), did not report any significant effect for GlcN-HCl in knee OA patients [18]. The question of the importance of GlcN formulation was addressed in the MA by Wu et al. [19]. The concluded that GlcN-H was ineffective for pain reduction in patients with knee OA. GlcN-S may have function-modifying effects in patients with knee OA when administered for more than 6 months. However, it showed no pain-reduction benefits after 6 months of therapy.

Finally, it is also important to consider the analysis of the RCTs provided by the Osteoarthritis Research Society International (OARSI) in its recommendations to interpret both the symptomatic and structure-modifying effect of GlcN. It analyzed 19 RCTs (16 of them with GlcN-S and 3 with GlcN-HCl) [8]. It reported an ES for pain of 0.46 (0.23 – 0.69), traducing a moderate symptomatic effect even if it decreased since the last analysis (0.61 (0.28 – 0.95) [6]). However, it revealed a strict difference between GlcN-S (ES for pain 0.58 (0.30 – 0.87)) and GlcN-HCl (-0.02 (-0.15 to 0.11)). In addition, ES of GlcN-S for pain tended to decrease when considering only high quality clinical trials (0.29 (0.003 – 0.57)). It also reported an ES on the reduction of joint space narrowing (JSN) of 0.24 (0.04 – 0.43) for GlcN-S on knee OA but no effect on hip OA.

2.1.2. Chondroitin sulfate (CS)

As with GlcN, CS has also been evaluated in different clinical trials to document both its symptomatic potential and its structure-modifying effect. The symptomatic efficacy of CS in knee OA has been proven [16]. In addition, a highly purified CS formulation (800 mg/day) produced symptomatic effect in hand OA [20]. A recent study [21] demonstrated a similar efficacy of CS on symptoms (pain on VAS and LI for function) when administered as a single daily dose of 1200 mg or three times a day at 400 mg. The authors concluded at an efficient and safe intervention. Interestingly, CS produced a significant reduction in joint swelling and effusion during the GAIT study [18].

A significant DMOAD effect for CS has been reported in RCTs. It was shown to produce a reduction of JSN [22], a significant difference in mean and minimal JSW [23] and a significant difference in joint space surface and mean JSW [24]. The MA by Hochberg et al. [25] and its update including studies of 2-year duration [26] demonstrated a modest but significant effect of CS (800 mg/kg) on the rate of decline of the minimum JSW. The MA by Lee et al. concluded at a delay of disease progression by CS [14]. A recent clinical trial, not yet included in MAs reported a symptomatic effect of CS (800 mg/day) combined with a reduction of the cartilage volume loss, bone marrow lesions and synovitis in knee OA patients [27].

The analysis provided in the OARSI guidelines [8] determined an ES of 0.75 (0.50 – 0.99) on pain and of 0.26 (0.16 – 0.36) for JSN but mentioned the industry bias that could exist and the heterogeneity of the results. If all studies are considered, the ES on pain of CS (0.75 (0.50 – 1.01)) was higher than those reported for GS (0.58 (0.30 – 0.87)) and especially for NSAIDs (0.29 (0.22 – 0.39)). This last consideration is important since we know the severe adverse effect induced by the long-term use of NSAIDs in OA patients. Clearly, the

risks/benefits balance seems to be in favor of CS. This should be considered at the time of therapeutic decision in the daily practice.

2.1.3. *GlcN and CS in combination*

While administered alone, neither GlcN-H nor CS produced any clinical effect during the GAIT study. However, the combination (GlcN-HCl 500 mg–CS 400 mg; three times a day) was shown to be efficient for pain relief and function improvement in OA patients with moderate to severe knee pain [18]. This finding suggests that a combination of GlcN and CS could be more efficient than CS or GlcN administered alone. Recently, the effects of GlcN/CS combination on progression of structural changes in knee OA was evidenced in a sample of the National Institutes of Health Osteoarthritis Initiative (OAI) longitudinal cohort. In participants taking a combination of GlcN and CS, the loss of cartilage volume over 24 months was reduced in some subregions when the assessment was made with quantitative magnetic resonance imaging (qMRI), arguing for a disease-modifying effect of GlcN and CS combined [28]. Finally, a double randomized placebo-controlled clinical trial with 2-year follow-up of 605 patients with knee OA, demonstrated that after adjusting for factors associated with structural disease progression (gender, body mass index, baseline structural disease severity and Heberden's nodes), dietary supplement combination of GlcN and CS resulted in a statistically significant reduction of joint space narrowing compared to placebo while CS or GlcN alone were without effect [29].

2.2. *GlcN and CS in guidelines*

The European League Against Rheumatism (EULAR) and the 2010 OARSI guidelines for the treatment of symptomatic knee OA recommend CS and GS [5–8]. In contrast, the UK's National Institute for Health and Care Excellence (NICE) has recommended that these products should not be used, mainly for economical reasons, while the American College of Rheumatology (ACR) recommended GS and CS under certain conditions [4]. Recently, OARSI has released new guidelines based on previous OA guidelines, an update of the 2010 OARSI systematic review and a consensus of 13 experts from relevant medical disciplines using the RAND/UCLA Appropriateness method and Delphi voting process for consensus [30]. The experts' vote resulted in an uncertain appropriateness for CS and GS despite a good quality of evidence, a very low risk score, a moderate to high effect size (up to 0.75 for CS) and a high benefit score.

3. Discussion and conclusions

There is significant evidence in the published literature as reviewed here to support the promising DMOAD potencies of both GlcN and CS. Some MAs have evidenced these beneficial effects and these compounds are currently recommended by EULAR. In contrast, these products were not recommended by the recent OARSI 2014, ACR 2013 and NICE 2013 guidelines. In most European countries, these drugs are prescribed whereas in US, they are delivered over-the-counter and they are not of pharmaceutical grade. In 2008, OARSI published evidence and expert consensus-based recommendations for the management of hip and knee osteoarthritis (OA) Treatment with GlcN-S and/or CS was recommended for knee OA with the proviso that it should be discontinued if no response is apparent within 6 months, although both may have long-term structure-modifying effects as shown in previous clinical trials [31,32] and confirmed in later study [22]. In 2010, Zhang et al. [8] published an update of the evidence available for therapies used in the treatment of hip and knee OA. The highest level of evidence (1a) was available for CS, GlcN-S while glucosamine

hydrochloride (GlcN-H) received a lower level (1b). The effect size (ES; 95% CI), which measures the strength of efficacy comparing to placebo was 0.58 (0.30, 0.87) for GlcN-S and 0.75 (0.50, 1.01) for CS. These ES were considered as moderate and they were smaller in more recent and higher quality trials, but they were still clinically relevant and at least comparable to those of NSAIDs and superior to acetaminophen (paracetamol). Recently, OARSI has released new guidelines based on previous OA guidelines, an update of the 2010 OARSI systematic review and a consensus of 13 experts from relevant medical disciplines [30]. Treatments were recommended as appropriate, uncertain, or not appropriate for each subphenotype. Appropriate pharmacological treatments for specific clinical subphenotypes included acetaminophen (paracetamol), capsaicin, duloxetine, oral NSAIDs (COX-2 selective and non-selective) and topical NSAIDs. Treatments of uncertain appropriateness for specific subphenotypes included Avocado/Soybean unsaponifiables, CS, GlcN, diacerein, opioids and rosetip. Only riseridronate was considered as inappropriate. The experts' vote resulted in an uncertain appropriateness for GlcN and CS despite a good quality of evidence, a very low risk score, a moderate to high effect size (up to 0.75 for CS) and a high risk/benefit score. Oral NSAIDs, well known to possibly induce adverse events especially in older patients and in patients with digestive, cardiovascular, or renal comorbidities, were appropriate for individuals without comorbidities despite a high risk score and a benefit score in the same order of magnitude of SYSADOAs. Therefore, why this reluctance for GlcN and CS? Several hypotheses can be formulated: (1) non-European experts were not familiar with prescription SYSADOA and were faced with products sold over-the-counter with heterogeneous and non-pharmaceutical grade quality; (2) favorable results from clinical trials of the prescription products have been mixed and confused with those obtained in poorer quality studies and/or performed with over-the-counter lower quality products, causing high study heterogeneity; (3) there may be a gap between results from clinical trials performed on a subset of well-characterized OA patients and the effects observed by practitioners on a general population in the real life; (4) a lack of confidence of the experts for industry sponsored clinical trials (although this should apply to all drugs, since they are all developed by the industry). Therefore, the term "uncertain" associated to GlcN and CS must be well explained to practitioners. The OARSI experts themselves did not consider the term "uncertain" as a negative recommendation which could preclude the use of GlcN and CS. Rather, it requires a role for physician–patient interaction in determining whether such treatments may have merit in the context of their risk-benefit profile and the individual characteristics, co-morbidities and preference of the individual patient. In this context, CS and GS which show a favorable risk/benefit ratio should be considered especially for the treatment of older OA patients with co-morbidities limiting the long-term and/or recurrent administration of drugs like oral NSAIDs and paracetamol, that were considered appropriate but have a lower risks/benefits ratio. Recent MAs [33] and clinical trials [22,34–37] have suggested that GlcN-S, GlcN-H and CS may contribute to reduce the intake of NSAIDs or paracetamol. Exclusion of GlcN and CS from the therapeutic arsenal of OA patients carries the risk to increase iatrogenic damages due to the overuse of NSAIDs and analgesics that in some countries are delivered over-the-counter without medical control. It is the responsibility of practitioners to treat OA patients by integrating within their individual level analysis, the risks and benefits for each treatment, the individual's co-morbidities, the efficacy of the therapy (continuous assessment of the symptoms) and the patient's personal preference.

Therefore, the used of CS and GS is an individual patient/physician informed decision by scientific, medical and economical evidence.

Most of the authors of the literature cited recommend the use of pharmaceutical grade products rather than food supplements. They insist on the importance of the formulation and quality of GlcN [38,39] and CS [40,41]. In the same way of thinking, one may consider the use of GlcN and CS as a combination therapy. Moreover, much evidence has been gathered here that document the potential that both compounds could exert on joint tissues during OA. One may therefore foresee additional benefits if not merely a synergistic potency.

Contributors

YH has written the paper. MM and AM have reviewed it and checked the literature.

Competing interest

None.

Funding

None.

Provenance and peer review

Commissioned following a presentation by Yves Henrotin at the 2nd World Congress on Controversies, Debates & Consensus in Bone, Muscle & Joint Diseases, November 21–24, 2013, Brussels, Belgium; and externally peer reviewed.

References

- [1] Loeser RF, Goldring SR, Scanzello CR, Goldring MB. Osteoarthritis: a disease of the joint as an organ. *Arthritis Rheum* 2012;64:1697–707.
- [2] Samuels J, Krasnokutsky S, Abramson SB. Osteoarthritis: a tale of three tissues. *Bull NYU Hosp Jt Dis* 2008;66:244–50.
- [3] Conaghan PG. Osteoarthritis in 2012: parallel evolution of OA phenotypes and therapies. *Nat Rev Rheumatol* 2013;9:68–70.
- [4] Hochberg MC, Altman RD, April KT, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis Care Res (Hoboken)* 2012;64:465–74.
- [5] Zhang W, Doherty M, Arden N, et al. EULAR evidence based recommendations for the management of hip osteoarthritis: report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCSIT). *Ann Rheum Dis* 2005;64:669–81.
- [6] Zhang W, Moskowitz RW, Nuki G, et al. OARSI recommendations for the management of hip and knee osteoarthritis, part II: OARSI evidence-based, expert consensus guidelines. *Osteoarthritis Cartilage* 2008;16:137–62.
- [7] Zhang W, Moskowitz RW, Nuki G, et al. OARSI recommendations for the management of hip and knee osteoarthritis. Part I: Critical appraisal of existing treatment guidelines and systematic review of current research evidence. *Osteoarthritis Cartilage* 2007;15:981–1000.
- [8] Zhang W, Nuki G, Moskowitz RW, et al. OARSI recommendations for the management of hip and knee osteoarthritis. Part III: changes in evidence following systematic cumulative update of research published through January 2009. *Osteoarthritis Cartilage* 2010;18:476–99.
- [9] Jordan KM, Arden NK, Doherty M, et al. 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* 2003;62:1145–55.
- [10] Zhang W, Doherty M, Leeb BF, et al. EULAR evidence based recommendations for the management of hand osteoarthritis: report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCSIT). *Ann Rheum Dis* 2007;66:377–88.
- [11] Hochberg M, Chevalier X, Henrotin Y, et al. Symptom and structure modification in osteoarthritis with pharmaceutical-grade chondroitin sulfate: what's the evidence? *Curr Med Res Opin* 2013;29:259–67.
- [12] Wieland HA, Michaelis M, Kirschbaum BJ, Rudolph KA. Osteoarthritis – an untreatable disease? *Nat Rev Drug Discov* 2005;4:331–44.
- [13] Wandel S, Juni P, Tendal B, et al. Effects of glucosamine, chondroitin, or placebo in patients with osteoarthritis of hip or knee: network meta-analysis. *Br Med J* 2010;341:c4675.
- [14] Lee YH, Woo JH, Choi SJ, et al. Effect of glucosamine or chondroitin sulfate on the osteoarthritis progression: a meta-analysis. *Rheumatol Int* 2010;30:357–63.
- [15] Henrotin YE. Interpretation of metaanalyses: pitfalls should be more widely recognized. *J Rheumatol* 2012;39:1107–9.
- [16] Bruyere O, Pavelka K, Rovati LC, et al. Total joint replacement after glucosamine sulphate treatment in knee osteoarthritis: results of a mean 8-year observation of patients from two previous 3-year, randomised, placebo-controlled trials. *Osteoarthritis Cartilage* 2008;16:254–60.
- [17] Rozendaal RM, Koes BW, van Osch GJ, et al. Effect of glucosamine sulfate on hip osteoarthritis: a randomized trial. *Ann Intern Med* 2008;148:268–77.
- [18] Clegg D, Reda D, Harris C, et al. Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. *N Engl J Med* 2006;354:795–808.
- [19] Wu D, Huang Y, Gu Y, Fan W. 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* 2013;67:585–94.
- [20] Gabay C, Medinger-Sadowski C, Gascon D, et al. Symptomatic effects of chondroitin 4 and chondroitin 6 sulfate on hand osteoarthritis: a randomized, double-blind, placebo-controlled clinical trial at a single center. *Arthritis Rheum* 2011;63:3383–91.
- [21] Zegels B, Crozes P, Uebelhart D, et al. Equivalence of a single dose (1200 mg) compared to a three-time a day dose (400 mg) of chondroitin 4&6 sulfate in patients with knee osteoarthritis. Results of a randomized double blind placebo controlled study. *Osteoarthritis Cartilage* 2013;21:22–7.
- [22] Kahan A, Uebelhart D, De Vathaire F, et al. Long-term effects of chondroitins 4 and 6 sulfate on knee osteoarthritis: the study on osteoarthritis progression prevention, a two-year, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2009;60:524–33.
- [23] Michel BA, Stucki G, Frey D, et al. Chondroitins 4 and 6 sulfate in osteoarthritis of the knee: a randomized, controlled trial. *Arthritis Rheum* 2005;52:779–86.
- [24] Uebelhart D, Malaise M, Marcolongo R, et al. Intermittent treatment of knee osteoarthritis with oral chondroitin sulfate: a one-year, randomized, double-blind, multicenter study versus placebo. *Osteoarthritis Cartilage* 2004;12:269–76.
- [25] Hochberg MC, Zhan M, Langenberg P. The rate of decline of joint space width in patients with osteoarthritis of the knee: a systematic review and meta-analysis of randomized placebo-controlled trials of chondroitin sulfate. *Curr Med Res Opin* 2008;24(11):3029–35.
- [26] Hochberg M. Structure-modifying effects of chondroitin sulfate in knee osteoarthritis: an updated meta-analysis of randomized placebo-controlled trials of 2-year duration. *Osteoarthritis Cartilage* 2010;18:S28–31.
- [27] Wildi LM, Raynauld JP, Martel-Pelletier J, et al. Chondroitin sulphate reduces both cartilage volume loss and bone marrow lesions in knee osteoarthritis patients starting as early as 6 months after initiation of therapy: a randomised, double-blind, placebo-controlled pilot study using MRI. *Ann Rheum Dis* 2011;70:982–9.
- [28] Martel-Pelletier J, Roubille C, Abram F, et al. First-line analysis of the effects of treatment on progression of structural changes in knee osteoarthritis over 24 months: data from the osteoarthritis initiative progression cohort. *Ann Rheum Dis* 2013, <http://dx.doi.org/10.1136/annrheumdis-2013-203906>.
- [29] Fransen M, Agaliois M, Nairn L, et al. Glucosamine and chondroitin for knee osteoarthritis: a double-blind randomised placebo-controlled clinical trial evaluating single and combination regimens. *Ann Rheum Dis* 2014, <http://dx.doi.org/10.1136/annrheumdis-2013-203954>.
- [30] McAlindon TE, Bannuru RR, Sullivan MC, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthritis Cartilage* 2014;22(3):363–88.
- [31] Reginster JY, Deroisy R, Rovati LC, et al. Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomised, placebo-controlled clinical trial. *Lancet* 2001;357:251–6.
- [32] Pavelka K, Gatterova J, Olejarova M, et al. Glucosamine sulfate use and delay of progression of knee osteoarthritis: a 3-year, randomized, placebo-controlled, double-blind study. *Arch Intern Med* 2002;162:2113–23.
- [33] Leeb BF, Schweitzer H, Montag K, Smolen JS. A metaanalysis of chondroitin sulfate in the treatment of osteoarthritis. *J Rheumatol* 2000;27:205–11.
- [34] Lagnaoui R, Baumevielle M, Begaud B, et al. Less use of NSAIDs in long-term than in recent chondroitin sulphate users in osteoarthritis: a pharmacy-based observational study in France. *Therapie* 2006;61:341–6.
- [35] Herrero-Beaumont G, Ivorra JA, Del Carmen Trabado M, et al. Glucosamine sulfate in the treatment of knee osteoarthritis symptoms: a randomized, double-blind, placebo-controlled study using acetaminophen as a side comparator. *Arthritis Rheum* 2007;56:555–67.
- [36] Blotman F, Maheu E, Wulwik A, et al. Efficacy and safety of avocado/soybean unsaponifiables in the treatment of symptomatic osteoarthritis of the knee and hip. A prospective, multicenter, three-month, randomized, double-blind, placebo-controlled trial. *Rev Rhum Engl Ed* 1997;64:825–34.
- [37] Bertin P, Taieb C. NSAID-sparing effect of glucosamine hydrochloride in patients with knee osteoarthritis: an analysis of data from a French database. *Curr Med Res Opin* 2014;30:271–7.
- [38] Aghazadeh-Habashi A, Jamali F. The glucosamine controversy: a pharmacokinetic issue. *J Pharm Pharm Sci* 2011;14:264–73.
- [39] Block JA, Oegema TR, Sandy JD, Plaas A. The effects of oral glucosamine on joint health: is a change in research approach needed? *Osteoarthritis Cartilage* 2010;18:5–11.
- [40] Calamia V, Fernández-Puente P, Mateos J, et al. Pharmacoproteomic study of three different chondroitin sulfate compounds on intracellular and extracellular human chondrocyte proteomes. *Mol Cell Proteomics* 2012;11.
- [41] Volpi N. Quality of different chondroitin sulfate preparations in relation to their therapeutic activity. *J Pharm Pharmacol* 2009;61:1271–80.