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Literature Review

Chondroprotection Validation

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Introduction

Symptomatic OA is generally defined by the presence of pain, aching, or stiffness in a joint with radiographic OA. The age-standardized prevalence of symptomatic hand and knee OA is 6.8% and 4.9%, respectively, in Framingham subjects age ≥26 years. However, prevalence of symptomatic knee OA was 16.7% among subjects age ≥45 in the Johnston County Osteoarthritis Project, much higher than that reported in the Framingham Study. About 9% of subjects in the Johnston County study had symptomatic hip OA [1].

Taking into account these percentages, there is no doubt on how important is to prevent or treat this *pandemic* pathology.

Classically, anti-inflammatory drugs where the pharmacologically option to treat OA, but during the last years new solutions have been founded and they seem encouraging. One of these solutions is the cartilage protector's drugs that will be the subject of this manuscript.

A cartilage protector is a substance or chemical composite that delays OA progression and improves the joint function through the chondrocytes protection. They are included in a group called SYSADOAS (Symptomatic Slow Acting Drugs for Osteoarthritis) and are considered potentially as SDMOADs (Structure Disease Modifying Osteoarthritis Drugs).

Even if they don't repair the existent damage, they seem to delay and reduce the OA progression between 3 and 6 months; and to determine if they can modified the illness progression a longer period of time in needed (no less than 2 years and probably more than 3 years) [2].

There are asymptomatic patients with radiological OA and patients with pain and normal x-rays [3-5].

There isn't a correlation between clinical and radiological signs. The illness progression is variable; even if in the majority of cases in slow. Sometimes the symptoms improve with time and the radiological signs don't progress [2,6].

Due to the doubts or the hope on this treatment for OA and the difficulty to demonstrate its clinical efficacy a validation of them with a clinical evidence analysis is needed.

Medicine Based Evidence presents a sceptical attitude through the diagnostic, prognostic and therapeutic techniques; allowing to take the better decision to resolve the problem. The way to complete this procedure consists on establish a relevant clinical question; perform a daily literature research; evaluate critically the quality of the studies, take decisions and apply correctly the obtained conclusions to the analyzed clinical problem.

Following this method, a positive or negative reason to use cartilage protection with oral chondroitin sulphate and glucosamine sulphate or hyaluronic acid intra articular has been searched. From the systemic revision performed till October 2014, the following studies were included: M with a randomized group control (ECA), systemic revision (RS) and meta analysis (MA); judging their design, performance and exposition. We have also critically review the revisions that accomplished the DARE criteria (Database of Abstracts of Reviews of Effects, Centre for Reviews and Dissemination, York University)

All the ECA, RS and MA included were reviewed even if on this review we have only included the most important to reduce the number of references. We have also used all the published letters directed to the authors and their letters in response. Their number is big and the show how interesting and controversial is this subject.

A quality and clinical evidence been assigned following the GRADE system (Grades of Recommendation, Assessment, Development and Evaluation) [7], the Oxford Centre for Evidence-Based Medicine scale [8] and the critical evaluation of Narvy and Vangsness [9].

Table 1: Systematic revision (RS) and meta-analysis (MA) of the use of chondroitin sulphate (CS) in patients with OA.

Author Year	Joint	Type study Level EC	Included studies	Heterogeneity I^2	Results	Effect size TE (95% IC)	Conclusions
McAlindon 2000 [35]	Hip Knee	MA Level II	9 ECAs *vs* placebo	Significant	Various Pain Lequesne	0,96 (0,63-1,30) 0,86 (0,64-1,09) 0,63 (0,32-0,94)	Low quality studies
Richy 2003 [37]	Knee	MA Level II	8ECAs *vs* placebo	Moderate	VAS Lequesne WOMAC	-	Similar than SG Excellent inocuity
Reichenbach 2007 [31]	Hip Knee	MA Level II	20 ECAs/ECCAs *vs* placebo or no treatment	High I^2= 92%	Pain Adverse effects	0,75 (0,50-0,99) RR 0,98 (0,79-1,31)	Excellent inocuity
Monfort 2008 [36]	Hip Knee	MA Level II	5 MAs *vs* placebo or no treatment	High Significant	Pain Function ↘analgesics	Significant in 4 MAs and minimal 1 MA	Excellent inocuity
Hochberg 2010 [38]	Knee	MA Level I	3 ECAs *vs* placebo	No evidence I^2= 0	Narrowing joint line	0,23 (0,11-0,35)	Effective reducing narrowing joint line
Lee 2010 [84]	Knee	MA Level II	4 ECAs *vs* placebo	No evidence	Narrowing joint line	0,26 (0,13-0,39)	Delays rx OA progression
Wandel 2010 [86]	Hip Knee	MA Level II	3 ECAs *vs* placebo	Heterogeneity low	Narrowing joint line	0,13 (0,00-0,37) 0,08 (–0,08-0,25)	Compared to placebo it is not better
Schneider 2012 [148]	Knee	MA Level I	3 ECAs *vs* placebo	No evidence I^2 = 0	Lequesne	0,73 (0,28-1,28)	Symptoms effective Treatment in knee OA K-L II-III
Gallagher 2014 [50]	Knee	RS Level II	4 ECAs *vs* placebo	-	Narrowing joint line	Reduces cartilage lost in 3 of 4 studies	It can stop OA progression

ECCAs: Studies with a control group nearly randomized; Heterogeneity: low I2 = 25%; mild I2 = 50%; high I2 = 75%; RR: Relative Risk ; K-L: Kellgren-Lawrence OA degrees; Rx: X-rays

All the studies considered low quality and the published before the year 2000 were excluded.

Classically, the effect size (TE) expressed as a standardized mean difference of a therapeutic action performed on a patients group is considered trivial when it is < 0.20; small if it is between 0.20 and 0.49; mild between 0.50 and 0.80; and big if it is > 0.80 [10]. To Dougados et al. a score lower than 0.20 is poor, between 0.20 and 0.40 is minimal, and from 0.40 till 0.60 moderate and more than 0.60 is clinically pertinent [11].

The IMMPACT consensus says that, a TE of 0.20 is considered clinically relevant on patients with chronic pain and knee OA [12].

TE is statistically significant ($p < 0.05$) if 0 is not included in the Confidence Interval (IC).

Through the critical analysis perform on this manuscript and the recommendations performed by scientific societies like the SER (Rheumatology Spanish Society). The EULAR (European League Against Rheumatism), OARSI (Osteoarthritis Research Society International), etc., we have enumerate some conclusions to allow the use of this product on the day clinical practice based on their evidence.

Chondroitin Sulphate (CS)

Pharmacology

It belongs to the glycosaminoglycan's group, those are important structural components of the cartilage extracellular matrix organized in conglomerates of high molecular weight (proteoglycan) that represent approximately 50% of the hyaline cartilage. Proteoglycans contribute to determine the mechanical properties of the cartilage retaining water in the interior on the collagen matrix and allowing the characteristic answer to the charges loading. One step important on the arthritis process is the reduction of proteoglycans content on the cartilage submitting the collagen matrix to a bad mechanical function. The reduction of proteoglycans on the matrix it is due to the increase of the metalloproteinases activity: neutral, collagenases, gelatinases and estromelisine, allowed for the reduction of their specific inhibitors. CS action can be due to the stimulation of proteoglycan synthesis, hyaluronic acid and collagen type II and the reduction of the catabolic and anti-inflammatory activity; inhibiting inflammatory molecules as TNF-α, IL-1β, COX-2, PGE2, NFκB; proteolytic enzymes like metalloproteases 3, 9, 13 y 14, collagenase, elastase, phospholipase A2, catepsine B, aggrecanase 1 and 2; free radicals, nitric oxide and the chondrocyte apoptosis [13-17].

The use of CS in OA is justified on the results obtained on in vivo models that demonstrated that those exogenous sulphated glycosaminoglycan's present a positive effect on the chondrocytes metabolism; stimulating the collagen type II, proteoglycans and hyaluronic acid production with a possible positive influence on a degenerative joint illness induced experimentally.

CS also helps on the subchondral bone remodeling increasing the expression and osteoprotegerin production and it reduces the RANKL (osteoclast differentiator) [18,19].

The dose employed on the majority of the clinical studies oscillates between 800 and 1200 mg per day, during a minimum period of 3 months [20-24].

In patients with knee OA the oral dose of 800 mg /day produces almost the same effect tan a dose of 1200 mg/day [25-26], and the treatment performed during three months two times a year obtains the same results as a continuous one [25].

10% of the fraction absorbed is CS and 90% substances with a lower molecular weight [17].

Table 2: Effect size on the joint line, meta-analysis of Hochberg *et al.* [Hochberg *et al.*, 2010] from three randomised control studies where they employed the same CS during 2 years.

Author Year	Number of patients	Changes on the joint line Mean ± standard deviation		Mean difference mm (95% IC)	Effect size (95% IC)
		CS	Placebo		
Michel, et al. 2005 [22]	300	–0,045±0,48	0,07±0,56	0,12 (0,00-0,23	0,22 (0,01-0,45)
Sawitzke, et al. 2008 [47]	257	0,107±0,68*	0,166±0,68*	0,06 (–0,17-0,28)	0,09 (–0,24-0,42)
Kahan, et al. 2009 [39]	622	0,07±0,03	0,31±0,04	0,14 (0,06-0,21)	0,26 (0,11-0,42)
Total	1179	–	–	0,13 (0,06-0,19)	0,23 (0,11-0,35)

*Standard error; IC: Confidence interval

After taking orally CS, the maximum blood concentration is achieved four hours later. Mean life of CS is 15 hours, the stationary period is reached in 3-4 days, the time needed to obtain the maximum effect is 35 days and at least from 4 to 6 months are needed to obtain the maximal effect [13,27].

Analyzing the content of CS on 11 nutrition supplements on the USA market a deviation between 10 and 110% were found; only 4 of them contained less than the 40% announced on their label. This was confirmed on a second analysis of 32 products [28].

With the CS sell at the chemist happens something similar [29].

Using CS non standardized can modified the result of some studies [30]. Pharmaceutic CS are regulated and standardized and present a high quality although the nutraceutical ones are poorer due to the lack of regulation existing on them [29].

The relative risk of adverse effects is 0.99 (95% IC 0, 76-1, 31) [31,32]. CS till a dose of 1200 mg/day is a treatment secure and non-toxic [33]. The clinical improvement produced after administrating 1200 mg in one dose one time per day is similar to that dose taken three times per day [26].

Effect on the clinical symptoms

During the two last decades multiple clinical studies said that CS improves the symptoms and function on patients with an effect that is continued during some months after the treatment [34].

Those studies results and those obtained on the MA concluded that CS is better than placebo on the reduction of pain, increase of functional capacity, reducing the amount of pain killers taken [35-37,23] and on the satisfaction of faculty and patient [23] (Table 1).

Even though, those MA show that CS has a efficacy from poor to mild on the symptomatic OA treatment with an excellent security profile [34,38,39,22,36,31].

The Pain on knee OA patient was positively controlled between the 6th and 8th week of treatment [40].

On the other hand, there are authors with high quality and methodological studies that have demonstrated a little effect on OA treatment; they suggest that the CS benefice on pain in minimal [31].

On the GAIT (Glucosamine/ Chondroitin Arthritis Intervention Trial) essay [20], 20 studies were analyzed showing more favorable results than the glucosamine (0.58; 95% IC 0, 30-0, 87), the NSAIDS (0.29; 95% IC 0, 22-0, 39) and the COX-2 inhibitors (0.44; 95% IC 0, 33-0, 55) [31].

The result was statistically significant in 18 of them [31,41]. The methodology employed on this MA has been discussed [42,43].

Analyzing high quality studies of CS (Jadad 5) the effect size was not significant [32].

A symptomatic positive effect was seen in knee OA patients and also in patients with hand OA reducing pain and increasing function [44].

There were no differences seen in patients with low pain administrating CS, glucosamine, both, celecoxib and placebo [45,46].

The efficacy of CS reducing the symptoms is similar than SG, except for the detention of the OA progression that for CS was none [37].

Effects on the progression of OA

It has been studied if CS improved OA symptoms and stopped joint degeneration. After 2 years of treatment with CS the stabilization of the joint radiological line on knees was seen compared to the progression seen on the control group [39].

Patients with a joint narrow of the radiological line of less than 1 mm, didn't experimented a radiological [22] or clinical [31] improvement.

In a MA [38] and a ECA [47] the mean effect of the studies was determined; the author concluded that the administration of 800 mg of CS per day during 2 year, in patient with knee OA, has a small effect but with a high statistical significant reducing the lack of joint line compared to placebo [38] (Table 2).

After two years of treatment a small protection joint effect was seen but significant (TE 0.26; 95% IC 0, 13-0, 39; $p < 0.001$) [48].

The results of this MA are contradictory with the ones obtained by Richy, et al [37].

Using the MRI in patients with knee OA, it has been demonstrated that after 6 months of treatment with 800 mg of CS per day reduces the loss of cartilage volume compared to placebo; and associated to a reduction of the damage of the subchondral bone. Those findings suggest a joint protector effect of CS [49,50].

Take home messages

CS is considered as a SYSADOA in Europe but in USA is considered as a nutritional supplement. In 2014, 16% of the population with OA in UK consumed CS [51,52].

To conclude

- CS is a natural substance that can be recommended as an action treatment with slow, secure and efficacy action in OA with possible delayed effect of the illness.
- CS can be used preferable in early periods of OA because its effect in advanced stages is lower or none [46,53,31].

Table 3: Glucosamine contain per capsule on different commercial products [74].

Product	Contain on label (mg)	Glucosamine (mg)	Equivalent SG (mg)	% of the declare quantity
1	500	409	519	82
2	500	277	351	55
3	500	325	445	65
4	500	330	419	66
5	500	248	315	50
6	1500	634	804	42
7	500	233	295	41
8	500	298	378	60
9	500	231	293	46
10	500	274	348	55
11	500	238	302	48
12	500	169	214	56
13	500	262	332	52

- The pharmaceutic CS has a better quality that the nutraceutical ones [29].
- OARSI guide recommends the treatment with GS alone or combined with CS that can be symptomatic beneficious in patients with joint OA. If the patient doesn't see an improvement after 6 months of treatment it needs to be stopped. Level Ia evidence [54]. The recommendation strength was 63% (95% IC 44-82%), being the NSAIDS 93% and paracetamol 92% (> 4 g/day) [54].
- CS has a level Ib of evidence on efficacy which sustains their use as a treatment in patients with hip OA. The strength of its recommendation based on it is efficacy is level A and it is based in all the evidence and clinical experience existent [55].
- EULAR recommends the use of CS in patients with knee OA, with an A recommendation degree; through a level evidence Ia [56].
- ESCEO (European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis) places CS in the first treatment step in patients with symptomatic knee OA [57].
- SER (Rheumatologist Spanish Society) recommends CS with an A degree to improve the symptoms in patients with knee OA (pain, function, reducing painkillers taken: level IA evidence) (radiological progression: level IB evidence) (reducing the number of patients that will need a TKR: no evidence).
- The evaluative agency of New Technologies Lain Entralgo (Madrid) places CS as a second line treatment for OA after the paracetamol and with a maximum degree of recommendation (IA) [58].
- Its favorable security profile, its good tolerance with different doses and after medium and long treatment and the lower frequency of adverse effects similar to placebo, makes CS an option to be taken into account, desirable and useful on OA treatment [30].

Glucosamine Sulphate (SG)

Pharmacology

Glucosamine (hexamine; $C_6H_{13}NO_5$) is a natural amino monosaccharide that constitutes part from some glycosaminoglycan's like hyaluronic acid or keratin sulphate. It is placed on the hyaline cartilage extracellular matrix near the CS4 and the CS6, being the substrate to the cartilage proteoglycans biosynthesis; and can stimulate it [59]. It has an anti-inflammatory activity in OA, inhibiting mediators like the nitric oxide, the IL-1β, the cliclooxigenase-2, the metalloproteinases, and some cartilage destructors enzymes like the collagenases, aggrecanases, phospholipases A2 and lysosomal enzymes and the formation of other substances like the peroxide macrophage radicals [60-63].

Glucosamine reduces bone resorption and combined with CS increases the expression of OPG/RANKL with a positive effect on the OA subchondral bone modifications [64].

It has been speculated if CS action can be due to its conversion on SG [60].

It is produced and used in Europe as a drug or as a nutraceutical in USA.

There were differences between studies were they have employed SG pharmaceutical versus the produced as a nutraceutical supplement.

The relative risk of adverse effects is 0.97 (95% IC 0, 88-1, 08) [65,32]. It is contraindicated in patients allergic to seafood. Diabetic patients had taken SG need to be carefully controlled because it can modify the glucose blood levels [66].

Clinical symptoms effects

The administration of glucosamine is more controversial than CS. A critical point is that it can be used as glucosamine sulphate or glucosamine hydrochloride (HCG), with important differences between them [67,68].

Actually HCG cannot be recommended regarding the clinical existing data [69]. Some authors have employed glucosamine intravenous and intramuscular [70,71], or intra articular [72,73].

Other important aspect is the difference on the active principle quantity existent between the different commercials products (Table 3) [74,67], some patients can be taking suboptimal doses [75,74].

The problem is that the minimal effective dose is not known and in humans taking 1500 mg per day the plasmatic concentrations reached by the glucosamine are lower than the experimental ones in vitro and in animals [75-77].

There is a MA where they show that SG taken during 12 weeks doesn't reach the point of the minimal difference perception on patients with painful knee OA [40] (Table 4). The problem is that on the same analysis the authors concluded that paracetamol, SG and CS are efficient to achieve the pain reduction after 1 month of treatment. Only the NSAIDS orally or topic and corticosteroids present an effect compared to placebo after 1 month [40].

Two MA reported a moderate but significant result of the glucosamine on the symptoms [35], with a significant improvement on pain, mobility, Lequesne index and WOMAC [37].

Table 4: Systematic revisions (RS) and meta- analysis (MA) on the use of glucosamine sulphate on patients with OA.

Author Year	Joint	Study Type Level EC	Included studies	Heterogeneity I^2	Results	Effect size TE (95% IC)	Conclusions
McAlindon 2000 [35]	Hip Knee	MA Level II	6 ECAs *vs* placebo	Significant	Various Pain Lequesne	0,44 (0,24-0,64) 0,51 (0,05-0,96) 0,41 (0,14-0,69)	To exaggerate
Richy 2003 [37]	Knee	MA Level II	7ECAs *vs* placebo	Moderate	Narrowing joint line	0,41 (0,21-0,60)	Significant benefactions effects Excellent inocuity
Poolsup 2005 [82]	Knee	MA Level I	2 ECAs *vs* placebo	No heterogeneity significant	Pain Function Progression OA	0,41 (0,21-0,60) 0,46 (0,27-0,66) RR 0,46 (0,28-0,73	Long term efficacy on the improvement of symptoms and the detention of the OA progression
Reginster 2007 [78]	Knee	MA Level I	3 ECAs *vs* placebo	No heterogeneity	WOMAC	0,33 (0,17-0,49)	Small/medium effect but clinically acceptable
Vlad 2007 [67]	Hip Knee	MA Level II	15 ECAs *vs* placebo	I^2 = 80%	Pain	0,44 (0,18-0,70)	Big heterogeneity
Towheed 2009 [65]	All joints except TM	MA Level II	25 ECAs 20 *vs* placebo 5 *vs* NSAIDs	I^2 = 92%	Pain Lequesne Adverse effects	0,47 (0,23-0,72) 0,47 (0,12-0,82) RR 0,99 (0,91-1,07)	Better than placebo on pain and function
Lee 2010 [84]	Knee	MA Level II	2ECAs *vs* placebo	No evidence	Narrowing joint line	0,43 (0,23-0,62)	It can delay rx OA progression
Wandel 2010 [86]	Hip Knee	MA Level II	5ECAs *vs* placebo	Low heterogeneity	Pain Narrowing joint line	0,17 (0,05-0,28) 0,16 (0,00-0,25)	Compared to placebo it doesn't reduce pain and narrowing joint line
Wu 2013 [68]	Knee	MA Level I II	13 ECAs *vs* placebo	Pain I^2 = 82% Function No heterogeneity	Pain Lequesne (>24 weeks)	0,22 (–0,04-0,48) 0,36 (0,17-0,56)	No effect on pain After > 6 months it improves function
Gallagher 2014 [50]	Knee	RS Level II	3 ECAs *vs* placebo	-	Narrowing joint line	Reduce cartilage lost in 2 of the three studies	It can stop OA progression

Heterogeneity low I2 = 25%; mild I2 = 50%; highI2 = 75%; RR: Relative Risk; Rx: x-rays; TM: temporo - mandibular joint.

A Cochrane revision has confirmed that glucosamine has a superior effect than placebo with pain improvement of 28% and on the function of 21% (Lequesne Index). Although, the results were not statistically significant for the pain, the function and the stiffness on the WOMAC (TE pain -0.16; 95% IC-0, 36-0, 0-4).

Glucosamine was as secure as placebo on the number of adverse effects [65].

There is a MA [78] with three high quality studies where they have employed 1500 mg of SG per day [79-81], demonstrating that this treatment improves the symptoms on the patient with knee OA at medium follow-up (Table 5). Also through a MA of two high quality studies, Pools up et al., concluded that the treatment with 1500 mg of SG one time a day during 3 years improve the symptoms in patients with knee OA (95% IC 0.21-0, 60) [82].

Table 5: Effect size on the changeof the WOMAC values performed by Reginster [78] from the three randomised studies where the same SG has been employed with a dose of 1500 mg one time per day for more than 6 months.

Author year	Number of patients	Change on WOMAC score Mean ± standard deviation		Effect size♦ (95% IC)
		Glucosamine sulphate	Placebo	
Reginster, et al. [78]	212	229±347.5*	101±458.4*	0.32 (0.04-0.59)
Pavelka, et al. 2002 [80]	202	8.0±8.7	4.9±8,2	0.37 (0.09-0.64)
Herrero-Beaumont, et al.† 2007 [79]	210	12.9±14.1	8.2±16.0	0.31 (0.04-0.58)
Total	624	–	–	0.33 (0.17-0.49)

†estudio Glucosamine Unum In Die (once-a-day) Efficacy (GUIDE); IC: Confidence interval; ♦effect size > 0,00favorable to glycosamine* WOMAC.

SG controls better the symptoms than placebo and it is similar to acetaminophen [79].

The improvement persists between 6 months and 3 years suggesting a possible modification of the illness [80, 81].

Compared to NSAIDS, its action starts slowly between the 2nd and 3rd week but it has a better GI tolerance [83,81, 82, 37,65]. The effect is maintained till 2 months after stopping the treatment [83].

The combined administration of glucosamine and GS has been studied. On the symptoms of patients with OA its effect is between moderate to big compare to placebo [20], with a 10% higher answer than the celecoxib [46]. The problem is that the quality of the different publications makes think that those effects can be exaggerated [35]. There is no evidence proving that the combination of both products offer any advantage than using just one of them [2] (Table 6).

Effect on the progression of OA

There are two studies showing a joint protect or effect of the SG after taking 1500 mg of SG per day during 3 months [80,81].

Different studies showed a reduction of the joint line narrowing [37,82,65]. A joint protector effect was seen employing SG (TE 0.43; 95% IC 0, 23-0, 62; $p < 0.001$) [84,50].

After 8 years of follow-up 6.3% patients with SG treatment were operated of a TKR compared to 14.5% of the patients from the placebo group [57].

On the other hand, comparing the effects of glucosamine 500 mg three times per day, CS the combination of both, celecoxib and placebo during two years; no difference was seen on the delay of OA progression. Knees with a grade II Kellgren-Lawrence (K-L) treated

Table 6: Different effects of the chondroprotectors in patients with knee OA, compared to placebo, from the analysis of Black, *et al.* [2].

Product	Improvement in pain / function	Reducing painkillers intake	Narrowing of the joint line detention	Progression to TKR detention
Chondroitin sulphate	Results heterogeneity	Mixed evidence	Efficacy evidence	Non efficacy evidence
Glucosamine sulphate (SG)	Efficacy evidence	Non efficacy evidence	Efficacy evidence	Efficacy evidence
Glucosamine hidroclorure (HCG)	Non efficacy evidence	Non efficacy evidence	Non efficacy evidence	Non efficacy evidence
Glucosamine + chondroitin	Results heterogeneity	Efficacy evidence	Non efficacy evidence	Non efficacy evidence

showed an improvement compared to placebo but this didn't happen in patients with OA grade III.

The joint line narrowing was less when CS or GS was employed compared to the administration of both [47].

Pharmacokinetic studies reported lower glucosamine absorption when it is employed with CS [85].

There is a study where the authors said that GS and CS alone or combined presented a small benefice without clinical relevance on pain and narrowing of the joint line on hips and knees with OA [86]. But this study presents methodological mistakes [87,88].

After three years of treatment with SG the TKR incidence was reduced on a 57% during the following 5 years; this demonstrated that an effect size under 0.40 can be clinically significant [89].

SG has not showed effects on the symptoms and OA progression on patients with hip OA [90], the different results of GS on multiple joints, can be explained with the possibility of differences existent on the physiopathology of OA on different joints [91].

The administration of HCG doesn't show structural benefits on chronic painful knees [92].

On the other hand, patients with knee OA, a mixed treatment of 1500 mg of SG and 800 mg of CS in one time a day dose compared to SG, CS or placebo after 2 years creating a significant reduction of the joint line compared to the other three groups [45].

Take home messages

10% of the USA population consumed SG on 2007 increasing the selling of this product a 60% between 2003 and 2010 with a cost of 210000 millions of dollars [92]. In 2004, 16% of the UK population [51] with OA takes glucosamine and 20% of the Australian population in 2012 [93].

The mean treatment cost was $34.95 for 30 days of treatment, and $429.40 per year. The QALY cost was £21,335, the potential benefices are moderated. These estimations are not very precise [2]. In 2010 an economic analysis has showed an increase of the cost efficacy of €10.491 versus placebo and €13.835 against paracetamol, suggesting that SG is an effective therapeutic alternative compared to placebo and paracetamol primary OA knees [94].

To conclude

- OARSI guide recommends the treatment with SG alone or combined with CS and can result symptomatic beneficial on patients with knee OA. If there is not a response after 6 months of treatment it needs to be stopped. Level I EC [54].
- OARSI guide in 2008 recommends the use of SG and CS in patients with symptomatic knee OA and can have structural effects modifications of the illness. Level Ib EC [54].
- EULAR says that there aren't specific data of the use of SG as treatment in patients with hip OA. The recommendation strength evidence and clinical experience is 37.06 with a standard error recommendable [55].
- EULAR recommends the use of SG in patients with knee OA with an A degree of recommendation from an IA level of evidence and a TE between 0.43 and 1.02 [51].
- The Australian guide to the non-surgical hip and knee OA treatment recommends SG with a C recommendation degree [95].
- To the SER the treatment with SG has an A recommendation degree because it improves the symptoms in patients with knee OA (pain, function) and controls the radiological progression of a OA with a level Ia of evidence in both cases, with a level Ib of evidence to reduce the analgesic needs and without evidence to reduce the number of patients that will need a TKR.
- ESCEO (European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis) places the SG at the first step of treatment on patients with symptomatic knee OA [57].

Hyaluronic Acid (AH) Viscosupplementation

Hyaluronic acid is a non-sulphated glycosaminoglycan. It is the principal constitute of the synovial liquid with a concentration of 0.35 g/ml, and of a extracellular matrix layer of 1-2 μm thick at the cartilage surface. It works as a lubricant absorbing the loads and impacts. OA reduces the molecular AH weight. Its viscosity and its elastic module making them lost its mechanicals and rheological properties and increasing the vulnerability of the cartilage in front the loadings [96].

Pharmacology

Hyaluronic acid and sodium hyaluronate are known as hyaluronans. The hylan is a derivate of the AH, with multiple polymers. Those products are characterized with their molecular weight [97,98].

The AH native has a molecular weight of 4-10 MDa and the hylan 6-7 MDa. The products with a molecular weight between 0.5-1.5MDa can have an easy diffusion through the synovial interstitial matrix increasing its concentration and interacting with cells and reducing the inflammation [99].

In animal models, those products present a bigger efficacy than the ones with a molecular weight over 2.3MDa [100]. There is no evidence that this happens also in humans.

AH has an anabolizing and anti-inflammatory activity and increases the production of AH endogenous, glycosaminoglycan's and tissue metalloproteinases inhibitors. It inhibits the production of PGE2, nitric oxide, free radicals, estromelisine, Il-1 and reduces the proliferation, migration and phagocytosis of the leukocytes and the apoptosis. The concentration increases after the injection of AH, maintaining the effects during 6 months [99].

The different products existent on the market are different on its composition, production method, dose, biological characteristics and possible clinical results [101,102].

They are normally administered intraarticular (IA) but there are also orally products [103]. If the treatment is effective it can be used after 6 months.

It has been commonly used on the knee.

The relative risk of local adverse effects is 1.49 (95% IC 1, 21-1, 83) [104,32], and for the AH with high molecular weight 2.04 (95% IC 1, 18-3, 53) [32] and they are mainly pain and inflammation.

Effect on the clinical symptoms

The AH has an analgesic and anti-inflammatory action, reducing the symptoms of the OA. The short period effect of the AH is attributed to the normalization of the joint viscoelastic fluid. Long period effect of AH, is related to the restauration of the mobility, the decreasing of pain and the homeostasis rheological and metabolically of the joint. An important placebo effect has been also associated to the puncture-aspiration-injection manoeuvre [105].

On the Cochrane revision, the pain TE on the WOMAC scale oscillates between 1.22 (95% IC 0, 52-1, 93) favorable to the AH after 1-4 weeks of the injection and 1.04 (95% IC 0, 32-1, 75) after 14-26 weeks of injection. For the function the TE was 1.02 (95% IC 0, 42-1, 62) and 0.80 (95% IC 0, 24-1, 37) respectively [104].

The benefice of AH is time-variable. It doesn't have an immediate effect. Compared to the corticosteroids intraarticular in patients with knee OA TE was –0.39(95% IC –0, 65- –0, 12) favorable to the corticosteroids after 2 weeks ,4 weeks 0.01 (95% IC –0, 23-0, 21) and 8 weeks 0.22 (95% IC –0, 05-0, 49), similar to them at 12 weeks 0.35 (95% IC 0, 03-0, 66) and clearly better for the AH after 26 weeks 0.39 (95% IC 0, 18-0, 59) [106].

In aECA, there was a statistically difference between placebo and AH on reduction of pain, improvement of function, global satisfaction and the amount of painkillers taken [107].

In patients with knee OA, AH is efficacy after 4 weeks, TE de 0.31 (95% IC 0, 17-0, 45) reaches its peek after 8 weeks, TE de 0.46 (95% IC 0, 28-0, 65) and presents a residual effect detectable after 24 weeks, TE de 0.21 (95% IC 0, 10-0, 31) [108].

The action peek of the AH is bigger than the acetaminophen (0.14; 95% IC 0, 05-0, 23), NSAIDS (0.29; 95% IC 0, 22-0, 35) [108,32], and COX-2 inhibitors (0.44; 95% IC 0, 33-0, 55) [48]. The effect is maintained during some months [109-111].

AH has been employed in others joints like hip, ankle and painful shoulder.

Two low quality systematic revisions [112,96] and four ECAs [113-116] has studied the role of AH on hip OA. All the previous studies concluded that AH seems effective and secure.

There is a RS evaluating the effect of AH in ankle OA [117], they considered that AH can significantly improve the pain compared to saline fluid, exercise or arthroscopy

A RS [118], concluded that AH improves the pain but not the function and three ECAs [119-121] showing an improvement of pain and function without adverse effects but more studies are need to confirmed or not those conclusions.

The majority of those studies have been done in posttraumatic OA ankles not in primary OA ankles.

One ECA employed AH in OA shoulders. The study concluded that AH was clinically effective and well tolerated [122]. It has been also used in rizartrosis [123,101] and on temporo-mandibular OA [101].

There isn't an evidence favorably to the AH and its molecular weight after 12 weeks of follow-up [124].

Some clinical essays performed with high molecular AH present more consistent results on improvement of pain and function [125,126] than hialuronate sodium.

No clinical difference has been founded between employing hylan against hyaluronate [116]. The absence of a bigger efficacious of the hylan compared to the hyaluronates and its higher risk of adverse effects has made some authors not recommended it [127]. But this is not clear because hylan only needs one injection per year, some studies said that its adverse effects are similar to hialuronates and the improvement of the symptoms is maintained during 26 weeks [128,129].

The treatment with AH seems as effective as NSAIDS after 5 weeks of treatment [130] and as an injection of corticosteroids after 6 months [131], and more effective than NSAIDS after 9 months with economical-medical benefices and without an additional cost [39].

This efficacy is bigger in intermediate OA stages than in advances ones [132,133].The patient's age doesn't influence on the therapeutic AH response [87].

A MA concluded that AH has an innocuity similar than saline serum [134] and significantly greater than NSAIDS [130].

Effect on the OA progression

There is a study of Wang et al showing a favorable effect of AH on the cartilage volume lost [135]. There is where the authors said that more studies are needed to establish some conclusions [50].

Table 7: Cost-efficacy of some non-surgical options of treatment in patients with knee OA.

	Cost-efficacy (Cost/QUALY) USA Dollars	Author(s), year
Patients with knee OA will pay at maximum	1.200-5.700	Byrne, *et al.* 2005 [149]
Orthotic	6.000	Segal, *et al.* 2004 [150]
Reducing weight	11.000	Segal, *et al.* 2004 [150]
NSAIDS	15.000	Segal, *et al.* 2004 [150]
COX-2 inhibitors	71.000	Elliot, *et al.* 2006 [138]
Hyaluronic acid IA	14.000	Torrance, et al. 2002 [151]

Take home messages

A dose of AH of 60 mg/3 ml cost in UK between £213 and £248 [136]. In USA, the annual viscosupplementation cost per patient oscillates between $1700 and $3700 [137]. The cost per QUALY of the viscosupplementation in Canada was $14.000 (Table 7) [138].

It is not clear if the less need of injections employing hylan has positive cost-benefice ratio compared to hyaluronate sodium [139,140].

The viscosuppementation is approved by the FDA to be employed on knee OA.

To conclude

- Scientific evidence is limited on viscosupplementation [141].
- It seems that AH and hylans reduce pain and improve function.
- OARSI guide recommends AH on hip and knee OA (Level Ia)
- EULAR recommends AH use in patients with knee OA with a B recommendation degree [56].
- Australia guide recommends AH in knee OA with a C recommendation degree [95].
- To the SER the treatment with AH presents an A recommendation degree
- ESCEO (European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis) situates AH at the second step on the treatment of patients with knee OA [57].
- On the Mexican clinical guide practice AH is indicated as an adjuvant in patients that have experimented a poor answer to the NSAIDS and COX-2 inhibitors (Leve Ib EC) [142,143].

Final conclusions

- After revising the literature more high quality studies are needed.
- May be the chondroprotectors present a therapeutic effect that needs to be well probed.

  Their optimal indications and the patient's characteristics need to be defined to obtain the greater benefice from this treatment [146].
- EULAR says that SYSADOA (CS, SG, AH) are efficacy on the symptoms of patients with hip OA but the patients are not well defined and the size of the effect either [55].
- EULAR conclude that SYSADOA (CS, SG, AH) present symptomatic effects that modify the OA structure on patients with knee and hip OA [145].
- The British Primary Care Rheumatology Society situates the SYSADOA on the first line of treatment with the paracetamol and the loss of weight [146].
- The Mexican guide practice clinic says that there is a clinical evidence of Ia level [142], corrected to a level II in 2013 [143], reducing the pain and improving the function in OA joints.
- The use of chondroprotectors in patients with OA is a treatment option that needs to be agreed between the patient and the doctor after complete scientific, clinical and economical information [147].

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