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Original article

Oral hyaluronan for the treatment of knee osteoarthritis: a systematic review

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Summary. *Study Objectives:* Osteoarthritis (OA) is the most common chronic condition of the joints, affecting approximately 27 million of people in the US and its prevalence is predicted to grow. Recently, symptomatic slowacting drugs for osteoarthritis (SYSADOA) have been vastly studied and have generated considerable interest among clinicians and the public. In particular, the use of oral hyaluronic acid (HA) treatments for knee pain has been the source of much research and it is now widely adopted in the clinic for its safety and relative low cost. The aim of this study is to discuss the efficacy of oral HA in treating knee OA based on the most recent data from the literature as well as to encourage the use of objective measures to determine more effectively the efficacy of current therapies for knee OA. *Methods:* We searched the PubMed database up to 23/01/2018 based on data from randomized, double-blind, placebo-controlled trials, non-controlled trials and cohort studies conducted in adult subjects. The search words used contained the terms: oral hyaluronan (HA) and knee osteoarthritis (OA). We selected 15 relevant reports. The review was registered on PROSPERO (International prospective register of systematic reviews), registration number CRD42018104127. *Results:* Companies in Japan, US and Europe produced different oral supplements containing HA in various formulations, which have been tested in clinical trials. The vast majority of the studies analyzed found significant improvements of scores including VAS, WOMAC, JKOM and SF-36v2 in patients with moderate knee OA after short (1 – 4 months) daily treatments with oral HA preparations, compared to placebo-treated controls. Interestingly, few studies proposed the use of objective measures to evaluate the efficacy of HA treatments with ultrasonography and an isokinetic dynamometer, but they obtained modest and controversial results. *Conclusions:* Current clinical data on oral HA products for the treatment of mild to moderate knee OA are promising and in line with The European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) recommendation to use SYSADOA. However, more high-quality research with larger sample sizes and longer exposures to the oral treatment is needed to confirm these data. Particularly, more effort is required to standardize the treatments (final dose of HA, molecular weight of HA and presence of other active molecules) and to assess the results on patients with objective measures.

Keywords: Hyaluronic acid, Oral treatments, Dietary supplement, Knee, Osteoarthritis, Objective measures

Introduction

Osteoarthritis (OA) is the most common chronic condition of the joints, affecting approximately 27 million of people in the US and this number is predicted to grow (1). OA can affect any joint, but it occurs most often in knees, hips and hands. With OA, the cartilage and bones within a joint begin to break down and an inflammatory process occurs. These changes usually develop slowly and get worse over time. OA can cause pain, stiffness, and swelling, and can result in disability. Severe OA is treated by osteotomy or artificial joint replacement, whereas conservative treatments include intra-articular injection of hyaluronan (HA) (2). HA injections have been shown to improve symptoms in several clinical trials (3–6), although they present

some difficulties such as the presence of trained personnel, potential risk of infection (low frequency but high hazard) for patients who need to visit the hospital regularly to receive these injections and pain in some cases. In the meantime, dietary supplements such us HA, glucosamine, and chondroitin are commonly being prescribed and used in the population to treat mild OA of the knee. The international evidence-based guidelines agree that knee OA management requires both non-pharmacological, and pharmacological approaches (7) and suggest to initiate a background therapy with chronic symptomatic slow-acting drugs for osteoarthritis (SYSADOAs), such as HA (8). The use of oral HA treatments for knee pain has been the source of much research in the last years (9) (Table 1). The aim of this review is to discuss the efficacy of oral HA in treating knee OA in adult subjects based on the most recent data from the literature as well as to encourage the use of objective measures to determine more effectively the efficacy of current therapies for knee osteoarthritis.

Material and methods

A literature search was performed using as primary medical search engine the PubMed database considering all articles published up to 23/01/2018, the registered review protocol can be found at: https://www.crd.york.ac.uk/PROSPEROFILES/104127_PROTOCOL_20180910.pdf. The review was registered on PROSPERO (International prospective register of systematic reviews in https://www.crd.york.ac.uk/prospero/). The inclusion criteria were randomized, double-blind, placebo-controlled trials, non-controlled trials and cohort studies. We used the following search terms to search the PubMed register: "oral" "hyaluronan" "HA", "knee osteoarthritis" "OA". There were no language restrictions on articles for inclusion and we contacted the study authors to retrieve the full article where only the abstract was available. We selected 15 relevant reports, excluding non-relevant articles and works with no full article available. Information was extracted from each included trial in view of: (1) type of oral treatment with HA (oral formulation, dose of HA, length of the treatment, additional substances); (2) clinical endpoints (considering subjective measures using validated score systems, or objective measures). Finally, risk of bias of individual studies was considered both at study or outcome level. Parameters considered were: hierarchy of clinical evidence, sample size, quality of data reported and statistical analysis. Publication bias and selective reporting within studies

Table 1: Major companies and oral HA products in the market

HA Product	Company (Country)	Trials	References
Hyabest	Kewpie (Japan)	Sato T, 2009	(12)
		Tashiro T, 2012	(17)
Kojun	Everlife (Japan)	Nagaoka I, 2010	(14)
		Yoshimura M, 2012	(15)
		Yoshimura M, 2012	(16)
Kojun premium	Everlife (Japan)	Takamizawa, N, 2016	(23)
Hyal-joint	Bioiberica (Spain)	Kalman DS, 2008	(11)
Mobilee	Bioiberica (Spain)	Möller I, 2009	(13)
		Martinez Puig D, 2013	(18)
		Sola' R, 2015	(20)
		Sanchez J, 2014	(19)
Oralvisc	Bioiberica (Spain)	Nelson FR, 2015	(21)
Microbial fermentate	Viscos LLC (US)	Jensen GS, 2015	(22)
Syalox 300 plus	River Pharma (Italy)	Ricci M, 2017	(24)
Ialoral 1500	PharmaSuisse Labs (Italy)	Galluccio F, 2015	(25)

are likely to be affecting the selected literature for this review because of the small size of the trials reported and the quality of data in the articles

Results

Clinical trials testing oral HA for the treatment of knee OA

We searched the PubMed database up to 23/01/2018 based on data from randomized, double-blind, placebo-controlled trials, non-controlled trials and cohort studies (Figure 1). We found 17 studies listed in PubMed and additional 3 studies through manual searches of the bibliographies of previously published reviews (9,10). From this list, 4 articles were excluded because no full text was available, also after contacting the main authors, and one article was excluded because it was not reporting clinical data. In the end we selected the following 15 relevant reports (11–25). These clinical studies can be subdivided according to the company producing the oral HA treatments as in Table 1.

In Japan the company Kewpie produced the product Hyabest, hard capsules with a total HA of 240 mg daily (MW 900 kDa) derived from microbial fermentation. Hyabest has been tested in 3 different trials (12,17) in studies with 15-30 patients with knee OA assuming the test treatment daily for 1 to 12 months. Significant improvements in knee pain and stiffness were recorded in the HA group compared with the placebo group ($p < 0.05$) using the Japanese Knee Osteoarthritis Measure (JKOM) (17) tests (Figure 2). Sato et al. also reported significative improvements in the WOMAC test after HA, but only in patients with severe knee pain (12).

Still in Japan the company Everlife produced from chicken comb extracts the products kojun and kojun premium (25-72mg HA daily) that have been tested in clinical trials with 14 - 40 patients (14–16,23). VAS reduction in HA test groups was observed (15,23) (Figure 3), and in HA products in addition of physical exercise (14). Yoshimura and collaborators also showed a decreased urinary level of both cartilage-specific type II collagen (CTX-II) and bone-specific type I collagen (NTx) indicating that the test product is effective in inhibiting cartilage degradation and bone remodeling (16).

In Spain Bioiberica produced from chicken comb extracts Hyal-joint, Mobilee and Oralvisc (48-60 mg HA). A study with Hyal-joint (11) showed a significant improvement in WOMAC, VAS and significant decreases for some inflammatory cytokines. Oralvisc (21) indicated no evident improvement in WOMAC scores, but some in SF-36v2 scores. Interestingly 4 studies with Mobilee (13,18–20) used objective measures to evaluate HA efficacy. Moller et al. conducted a retrospective cohort study and showed reduction of synovial effusion after Mobilee intake using ultrasonography (13). This data was confirmed in an interventional trial by Sanchez and collaborators (19) (Figure 4). Of the three trials testing the isokinetic dynamometer, two found significant increase in muscular strength at isokinetic peak torque at 240° (18,19) (Figure 5) and one also at 180° (20), but only in men.

Of the remaining studies, the products from companies Viscos LLC in USA, River Pharma and PharmaSuisse Laboratories in Italy showed respectively mild decrease of pain scores in VAS (22), significant improvements in American Knee Society Score (AKSS) and VAS scores (24) and reduction of pain scores in VAS, but without a control group (25).

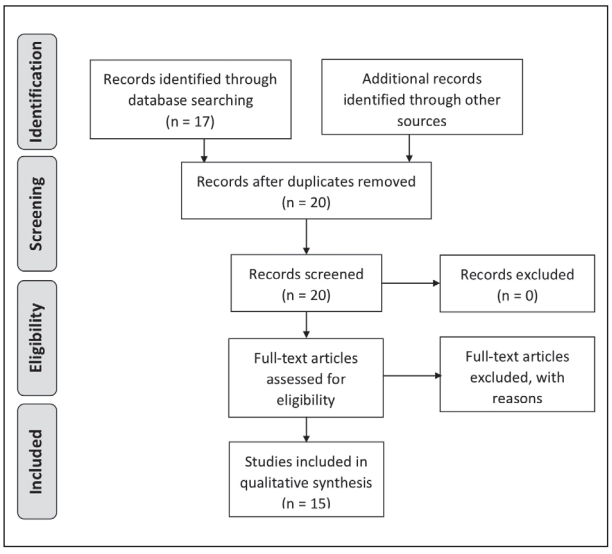

Figure 1: Flow diagram of information according to PRISMA 2009 (35).

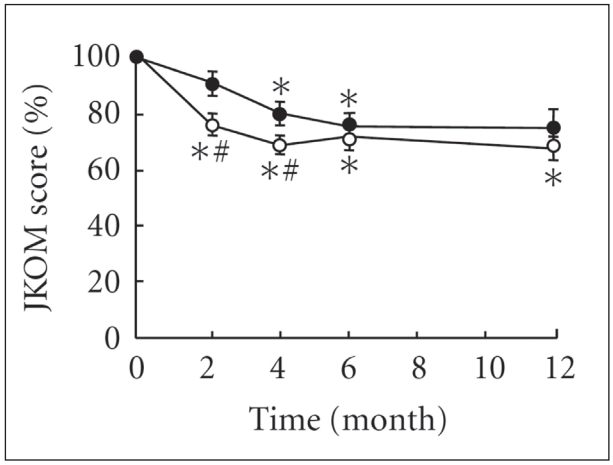

Figure 2: Change in the total Japanese Knee Osteoarthritis Measure (JKOM) score in younger patients (≤70 years of age; 21 subjects). ○hyaluronan; ○placebo. Values are presented as the mean ± SE. p< 0.05 vs. baseline; #p < 0.05 vs. placebo group (17).

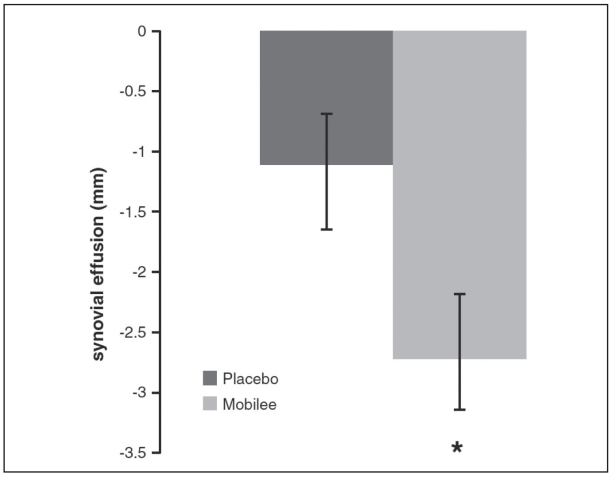

Figure 4: Ultrasonography of the knee investigated after a three-month treatment with Mobilee or placebo. Measure of synovial effusion compared to placebo group (mean ± SD, *p < 0.05) (19).

Discussion

HA preparations heterogenicity

HA is a high molecular-weight (MW) polysaccharide with a mean MW ranging from several hundred to several millions of Daltons (26). HA is present in every connective tissue and organ of vertebrates, in particular, is found with the highest concentration in synovial fluid (26,27). HA is used in clinical treatments of osteoarthritis (OA), mainly in two forms: intra-articular injections and oral administrations.

In the oral treatments there is a high heterogenicity in the composition of preparations employed differing for the MW of polysaccharides present, doses and addition of other active components.

In the clinical trials considered for this review, formulations with MW ranging between 900 kDa to 2.5 - 2.8 million Daltons have been used, with molecules of MW around 900 kDa being mostly adopted (Table 2). HA is not absorbed into the body as a high-molecular-weight polymer after ingestion. In 2016 Kimura et al. showed that orally administered HA is degraded to oligosaccharides by intestinal bacteria, absorbed in the large intestine and subsequently distributed in the body (28). Experiments on intestinal epithelia model cells showed that HA is rarely adsorbed at MW >7 × 104 and adsorption is higher at MW<5×103 kDa (29). In rats and dogs Balogh et al. reported that 99 mtechnetium-labeled HA at a MW of 1 × 106 was accumulated in tissues such as joints four hours after oral administration (30). Doses of oral HA preparations range from 20 to 120mg daily with different outcome on the clinical conditions of patients (Table 2). Finally, many dietary supplements containing HA

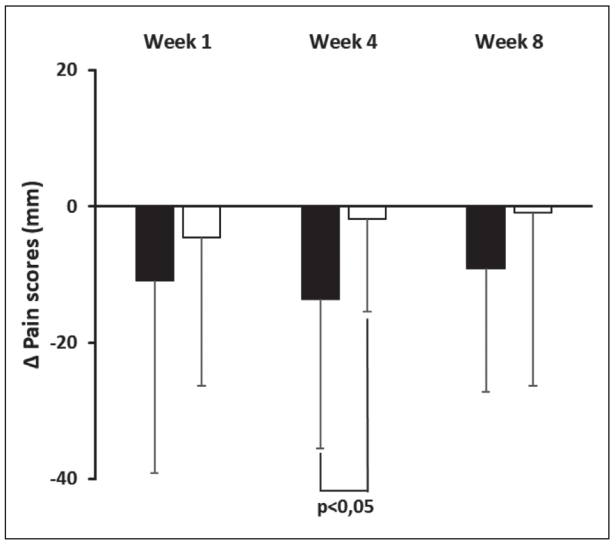

Figure 3: Changes from the baseline in the pain scores (VAS) for the dominant foot in the test and placebo groups during the 12-week intervention. Test group (closed bar) (n=19) and placebo group (open bar) (n=19), means ± standard deviation (adapted from 15).

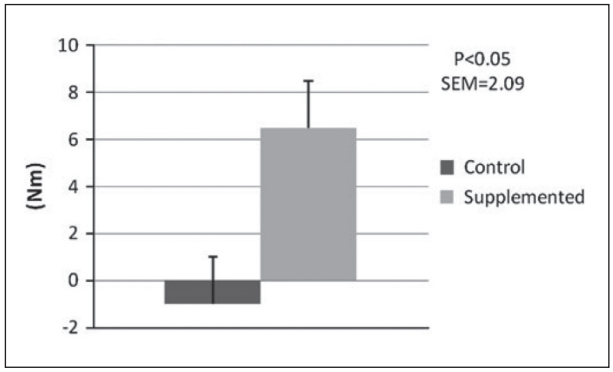

Figure 5: Isokinetic test of knee strength. Increase in maximum peak torque compared to baseline values (Nm) for knee extension at 240°/s. (18).

are enriched with other components such as collagen, other polysaccharides as glucosamine sulphate and chondroitin sulphate or vitamins, but the compounds are too many to be analyzed here and the focus of this work remains the HA component.

Objective measures to determine effective results

To date, the vast majority of studies that can be found in the literature used subjective measures to determine the efficacy of HA treatments. As shown in table 3, the most commonly used subjective measure is the VAS (visual analogue scale) (13–15,21–24). VAS is a psychometric response scale where volunteers can indicate a position along a continuous line between two end-points.

Along with the VAS also the WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) and SF-36v2 (the Short Form (36) Health Survey V2) are commonly used (table 3). The WOMAC and the SF-36v2 are two standardized questionnaires used by health professionals to evaluate the condition of patients with osteoarthritis.

Interestingly, a small number of studies with Bioiberica in Spain tried to improve the evaluation of HA effects on knee osteoarthritis by using some objective measures such as ultrasonography and an isokinetic dynamometer (13,18–20). In particular, ultrasonography has several advantages: It provides images in real-time, it is safe and relatively cheap. Moreover, some clinical trials found an association between ultrasonography measures and VAS scores, the WOMAC index, and medial knee pain (31,32). Nevertheless, ultrasonography has some disadvantages: standard scoring systems have not been extensively studied (33) and it relies heavily on the skills of the operator.

The isokinetic dynamometer is a quite complicated technique: it requires a Biodex system (Biodex Medical Systems, New York, USA) with five repetitions at two angular velocities (180°/s and 240°/s). The subjects assume a sitting position with the hips flexed at 90° and the maximum work load (J), maximum peak torque (Nm) and power (W) at 180°/s and 240°/s are measured.

Table 2: Composition of products in included articles

Product	Composition	References
Hyabest	HA at 240 mg (MW 900 kDa) MF	(12,17)
Kojun	HA mixture with propolis extracts, vitamins etc. at 1,800 mg (HA 27 mg) CCE	(14)
	HA mixture at 4,800 mg (HA 72mg) CCE	(15,16)
Kojun Premium	HA mixture (HA 25.2 mg) CCE	(23)
Hyal-Joint	HA mixture with collagen and other polysaccharides (HA 48 mg; MW 1000 kDa) CCE	(11)
Mobilee	Mobilee 80mg (HA 48-60mg) CCE	(13,18-20)
Oralvisc	HA mixture with GAGs at 80mg (HA 56mg) CCE	(21)
Microbial fermentate	HA 45mL (MW 2.5 - 2.8 million Daltons) MF	(22)
Syalox 300 plus	HA 300 mg, Boswellia serrata extract 100 mg, AKBA 10mg MF	(24)
Ialoral 1500	HA, CS, keratin matrix, manganese, and piperine (HA 120mg) MF	(25)

CCE = chicken comb extract

MF = microbial fermentation

The studies that have adopted this technique showed contrasting and modest positive results in the HA treated groups compared to the control groups. This may be due to the fact that in patients with OA, the excess of synovial fluid could produce pain and therefore interfere with isokinetic assessment of the muscular strength.

Conclusion

Knee OA is a common problem in the population and the number of patients affected by this condition is increasing. The use of oral HA preparations is now widely adopted because of its safety and relative low cost. Various clinical studies have shown moderate efficacy of oral HA treatments in reducing pain and improving knee functionality, with no side effects.

However, several limitations affect current literature on the subject: different efficacy end points, dosages of HA from 25 to 300mg and mixture with other components, molecular weights from 900 kDa to 2.8 MillionDa. Moreover, the quality of results is also reduced by generally low sample size groups and short duration therapies. The European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) recommends a chronic background therapy of several months, but only one of the examined studies prolongs the treatment with HA over 6 months (17).

Finally, most of these studies have adopted subjective measures, such as VAS and WOMAC scales, to evaluate oral HA efficacy. Objective measures to determine effective results were rarely used in the analyzed clinical trials (4 out of 15 studies) and obtained modest and controversial results. In particular, these methods were not able to directly quantify patient's quality of life.

In the analyzed trials the range of motion (ROM) of the knee joint measured with a goniometer was never used as end point. Although this is not considered the best method of assessing patients' disability in severe OA (34), this simple and objective measurement remains a frequently used tool in daily practice by orthopedics and it could be easily correlated with specific scales like VAS and WOMAC to improve the patient evaluation.

To conclude, the current clinical data on oral HA products for the treatment of mild to moderate knee OA are promising and in line with ESCEO recommendation to use SYSADOA. However, more highquality research with larger sample sizes and longer treatments (over 6 months) with the oral preparations is needed to confirm this data. Moreover, further work is necessary to standardize the oral treatments of HA in formulations and doses and to assess the clinical outcomes with objective measures.

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Table 3: Major endpoints measured in included articles

Endpoint	Number of articles	% of articles	References
VAS	7	47	(13–15,21–24)
WOMAC / JKOM	5	33	(11,12,17,21,25)
SF-36v2	3	20	(11,18,19)
Isokinetic dynamometer	3	20	(18–20)
Ultrasonography	2	13	(13,19)
Other	4	27	(14,16,18,24)

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