applied sciences

MDPI

Review

Viscosupplementation in the Therapy for Osteoarthritic Knee

Junghyun Park [1], Hue Jung Park [2], Min Cheol Rho [2] and Jin Joo [2,*]

[1] Department of Anesthesiology and Pain Medicine, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Incheon 21431, Korea; happyjj@catholic.ac.kr
[2] Department of Anesthesiology and Pain Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul 06591, Korea; huejung@catholic.ac.kr (H.J.P.); happyingpooh@naver.com (M.C.R.)
* Correspondence: jiyo1004@catholic.ac.kr

Abstract: Osteoarthritis (OA) is a degenerative disease that is spreading worldwide due to an aging population. This is not simply a disease caused by worn out joints, but a complex disease accompanied by various mechanisms such as inflammatory reactions. Among various joints, knee joints show degenerative changes earlier than other joints because they carry most of the weight load, causing social-economic problems. In the case of OA of the knee that does not respond to relatively simple conservative treatments such as physical therapy or medication, intra-articular injection is preferred. However, intra-articular injection drugs have limited effectiveness and uncertainties. There are several intra-articular viscous supplement drugs such as hyaluronic acid. Tissue regeneration active materials such as polydeoxyribonucleotide and polynucleotide are also newly used. The objective of this paper was to compare effects of intra-articular supplementation drugs used for degenerative arthritis of the knee.

Keywords: osteoarthritis; knee viscosupplement; hyaluronic acid; cross-linked hyaluronic acid; polydeoxyribonucleotide; polynucleotide

check for updates

Citation: Park, J.; Park, H.J.; Rho, M.C.; Joo, J. Viscosupplementation in the Therapy for Osteoarthritic Knee. *Appl. Sci.* **2021**, *11*, 11621. https://doi.org/10.3390/app112411621

Academic Editor: Marta Erminia Alberto

Received: 25 October 2021
Accepted: 29 November 2021
Published: 7 December 2021

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Copyright: © 2021 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

1. Introduction

Osteoarthritis (OA) is a disease in which inflammation of the cartilage and synovial membrane causes exudate in the joint cavity, stiffness, swelling, and joint pain [1]. According to data analysis in the United States, 54.4 million adults were diagnosed with OA between 2013 and 2015. If this trend continues, it is estimated that 78.4 million adults will be diagnosed with OA by 2040 [2]. The social cost of OA is at a level that cannot be ignored.

OA is a disease that cannot be explained by simple degenerative changes. It is a disease caused by several complex factors, such as genetic changes and lack of sex hormones [3]. Recent studies have focused on molecular markers caused by chondrocyte aging [4]. Although various treatment methods for OA have been suggested, there is a limit to clearly selecting one treatment method due to its complex pathophysiology. Non-pharmacologic modalities such as physical exercise and rehabilitation have been recommended for the treatment of knee OA. Oral drugs are also used when effects of non-pharmacologic modalities are limited. Various drugs ranging from non-steroidal anti-inflammatory drugs (NSAIDs) to opioids are used for OA treatment [5].

Since these oral medications can cause systemic side effects, intra-articular injection has been continuously increased to minimize systemic adverse effects and enhance local effects. Injecting drugs into the joint cavity is increasingly used recently. These drugs include steroids, hyaluronic acid (HA), and cross-linked hyaluronic acid (CL HA), polydeoxyribonucleotide (PDRN), and polynucleotide (PN). This review article aims to summarize effects and evidence of intra-articular injections, especially viscosupplements, in patients with knee OA. Steroids, analgesics, and platelet rich plasma (PRP) were excluded.

We searched the databases PubMed, PubMed Central, Medline, Google Scholar, and Google using the key words "viscosupplement", "intra-articular supplement", "hyaluronic

acid", "cross-linked hyaluronic acid", "polydeoxyribonucleotide", and "polynucleotide", along with key words adapted for individual condition (eg, knee osteoarthritis, knee OA). Our selection criteria gave precedence to systemic review, guidelines, meta-analyses, and large, randomized trial. There are not many papers on PN/PDRN for the treatment of OA, so retrospective observational study and open label study were also included. We excluded non-English articles, animal studies, and articles on osteoarthritis of the wrist, hip, and ankle. Platelet rich plasma (PRP) was also excluded, because most of the papers compared the non-inferiority of PRP to HA and CL HA.

This review was conducted based on 128 papers (HA 84 papers, CL HA 28 papers, PDRN/PN 16 papers) that satisfy the above criteria out of a total of 10,000 papers.

2. Hyaluronic Acid

In the 1980s, a substance called polyvinylpyrrolidone (PVP) hyaluronate was developed in Russia that could replace synovial fluid. This was administered to OA patients. It was reported in 1984 that PVP hyaluronate injected into the joint space had anti-inflammatory, prolonging, and anti-commissural effects as well as lubricating effects without major side effects. In 1997, the US Food and Drug Administration (FDA) approved viscosupplementation as a conservative technique for the management of OA [6]. The structure of HA is shown in Figure 1 [7]. Since then, until the early 2000s, articles have been published, showing that hyaluronic acid (HA) is more effective in OA compared to the control group (saline group) or that it is non-inferior to previously used corticosteroid (CS) intra-articular (IA) injection. After 2010, papers comparing new HA with existing drugs have been published. Since late 2010, articles have been published, claiming that new substances such as PRP are non-inferior to HA. Most articles have proved that HA is effective for OA, although some papers have reported that there is no difference in efficacy between HA and the control group. Research papers comparing the efficacy of HA with other drugs or treatments from 1984 until recently are summarized in Table 1.

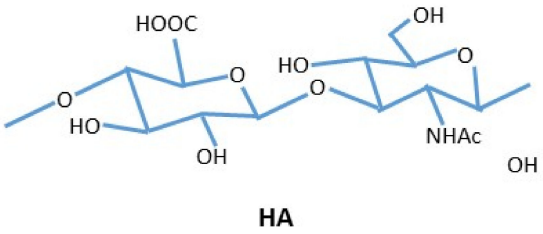


Figure 1. Structural formula of hyaluronic acid (HA) [7].

Table 1. Clinical studies evaluating the efficacy of intra-articular hyaluronic acid (IA HA) in OA (except cross-linked HA).

Publication Year [Ref.]	Study Design	Comparison Agent	Patients Number (Treat/Control)	Injection Times	Result
1987 [8]	RCT	saline	34(17/17)	3	Significant difference compared to control group in all variables of spontaneous pain intensity, tactile sensation, load, and pain when walking at 60 days first post-injection
1991 [9]	RCT	MPA	40(20/20)	3	When comparing the HA group and the MPA group, the analgesic effect was the same during the treatment period, but the analgesic effect at 45 days after the end of treatment all the pain monitoring parameters presented significant differences in favor of the HA-treated group
1993 [10]	RCT	0.25 mg HA/2.5 mL	209(102/107)	5	LI showed a significant superiority of the Verum-treated patients after the third injection until 9 weeks. The consumption of paracetamol did not reveal significant differences between the treatment groups
1994 [11]	RCT	saline	91(45/46)	5	No significant benefit compared to placebo group
1995 [12]	RCT	TA	63(32/31)	5	Significantly less pain was experienced by the HA group during the 6 months follow-up period
1996 [13]	RCT	saline	189(96/93)	5	Patients with knee OA over 60 years of age and high degree of knee OA have a greater therapeutic effect of IA HA injection

Table 1. *Cont.*

Publication Year [Ref.]	Study Design	Comparison Agent	Patients Number (Treat/Control)	Injection Times	Result
1998 [14]	RCT	saline	495(248/247)	5	HA group, VAS decreased by 2 or more (5~26 weeks). In the HA group about half of the group had mild pain or no pain at week 26 (about 30% of the naproxen group). There was also less pain when walking.
1999 [15]	RCT	saline	50(25/25)	5	Pain during walking, VAS, LI: Proved that the HA group was superior with a significant difference at 5 weeks and 6 months F/U
2001 [16]	RCT	saline	226(113/113)	3	WOMAC, pain on standing were improved from Weeks 7 to 27
2002 [17]	RCT	saline, NSAID	120(30/30/30/30)	3	IA HA + p.o. placebo vs. IA HA + p.o. NSAID vs. IA placebo + p.o. NSAID vs. IA placebo + p.o. placebo: For resting pain relief, HA seems to be as effective as NSAIDs. For pain with physical activity and functional performance, HA may be superior to placebo alone or NSAIDs alone.
2003 [18]	RCT	saline	408(204/204)	3 (2 cycle: total 6)	No superior effect compared to placebo group (in mean joint space width)
2004 [19]	RCT	saline	240(120/120)	5	WOMAC pain, stiffness improved compared to placebo group
2005 [20]	RCT	arthrocentesis	374(128/120/124)	4	HAX4 (O4), HAX3+ Arthrocentesis 1 time (O3A1), or 4 arthrocenteses (control group, A4). More O4 patients improved their WOMAC pain scores by more than 40% compared to A4.
2006 [21]	RCT	saline	106(53/53)	3	WOMAC, VAS improved compared to placebo group
2007 [22]	Clinical study	Home exercise program	60(20/20/20)	5	HA 5 times vs. HA 3 times vs. HA 3 times + exercise: HA 3 times + exercise group significantly faster onset of pain relief compared with other group: WOMAC, VAS improved in all groups
2008 [23]	RCT	saline	20(10/10)	8	WOMAC, VAS improved compared to placebo group
2009 [24]	RCT	saline	588(293/295)	3	WOMAC, pain, QOL improved compared to placebo group
2010 [25]	RCT	saline	48(24/24)	3	WOMAC, VAS improved but there was no statistically significant difference in functional and symptom improvement with respect to placebo
2010 [26]	RCT	CS	51(26/25)	5	VAS improved both groups; measured joint fluid levels of HA, biomarker: IA HA may have protective effects on the articular cartilage by increasing the HA concentration in synovial fluid, inhibitory effects on the catabolism
2011 [27]	RCT	saline	306(153/153)	5 (4 cycle: total 20)	Received four cycles of five IA HA or placebo injections: repeated cycles of IA HA not only improve knee OA symptoms during the in-between cycle period but also exert a marked carry-over effect for at least 1 year after the last cycle.
2011 [28]	RCT	saline	200(100/100)	5	WOMAC, pain 50-foot walking test improved compared to placebo group
2012 [29]	RCT	saline	30(15/15)	3	Old age (mean age: 72), The overall effect of HA on gait velocity in older knee OA patients was not significant compared to placebo.
2012 [30]	RCT	MPA	391(130/129/132)	3	HAX1 vs. HAX2 vs. MPS 40 mg 1 time: Both IA HA regimens were effective in relieving pain: did not show a difference vs. IA MPA
2014 [31]	Randomized, open-label	NSAID	184(98/86)	5	HAX5 vs. NSAIDs 3 times per day for 5 weeks: early efficacy of IA HA is suggested to be not inferior to that of NSAIDs, and that the safety of the early phase of IA HA is superior to that of NSAIDs for patients with knee OA.
2015 [32]	RCT	saline	196(98/98)	3	HA was not superior to placebo.
2019 [33]	RCT	HA + CS CS	44(16/16/12)	3	In HA alone group, WOMAC, knee extensor and flexor strength improved, but not proprioception

WOMAC, The Western Ontario and McMaster Universities Osteoarthritis Index; LI, Lequesne Index; OA, osteoarthritis; MPA, methyl-prednisolone acetate; CS, corticosteroids; TA, triamcinolone acetate; IA, intra-articular; HAX1, HA 1 time; HAX2, HA 2 times; HAX3, HA 3 times; HAX4, HA 4 times; HAX5, HA 5 times.

Table 1 summarizes 25 RCTs and 1 clinical study that showed meaningful results among a total of 250 IA HA papers searched. In 3 studies, it was revealed that there was no difference in efficacy compared with the saline control group, and 23 papers reported that it was superior to the saline control group or there was no difference in efficacy compared to the IA steroid group or the NSAID oral administration group.

Since the 1990s, many review articles on effects of HA have been published. Some review articles have reported that HA is ineffective in improving knee pain and function in patients with OA of the knee. However, there are more papers reporting that it is effective in improving knee pain and function with OA of the knee.

When looking at meta-analysis of the efficacy of some control groups (saline or arthrocentesis), the control group is also reported to have efficacy. Thus, it is necessary to consider the placebo effect [34]. As mentioned above, studies on knee OA, knee intra-articular supplement, hyaluronic acid review, or systemic review were searched in several search databases such as PubMed, PubMed Central, and Medline. Among 147 articles searched for, articles on effects of other drugs such as PRP and ozone were excluded under the premise that HA was effective. Furthermore, papers on OA in areas other than the knee were excluded. Among papers published from 1993 to 2021, 12 papers reported a negative effect of HA on knee arthritis, 66 papers reported a positive effect of HA, and 12 papers reported some positive or partially negative effects of HA. Major review articles about effects of HA on knee OA are summarized in Table 2. Table 2 summarizes well-organized 12 meta-analysis and 11 systematic reviews among the searched review articles for a total of 98 IA HA. Four papers revealed that IA HA had no statistical significance in the improvement of knee arthritis compared to the control group. In 19 papers, it was reported that it was effective in improving knee arthritis compared to the control group, and there was no difference in efficacy compared to the IA steroid or NSAID oral administration group.

Table 2. Review articles evaluating the efficacy of intra-articular hyaluronic acid (IA HA) in knee osteoarthritis.

Publication Year [Ref.]	Study Design	Pro/Cons	Result
2006 [35]	Systemic review	pro	5 to 13 weeks post injection period which showed improvement for pain and function. Comparable efficacy was noted against NSAIDs and longer-term benefits were noted in comparisons against IA CS
2010 [36]	Systemic review	pro	HA is more effective than the placebo group without major side effects. It is similar to CS in terms of effect.
2011 [37]	Meta-analysis	pro	IA HA is efficacious by 4 weeks, reaches its peak effectiveness at 8 weeks and exerts a residual detectable at 24 weeks.
2015 [38]	Meta-analysis	pro	Acetaminophen, diclofenac, ibuprofen, naproxen, celecoxib, IA CS, IA HA, oral & IA placebo. Comparing 2 or more; most efficacious treatment is IA HA, the least efficacious treatment is acetaminophen
2015 [39]	Systemic review	pro	ESCEO 2014 Short-term weekly HA injections are effective for up to 6 months.
2015 [40]	Meta-analysis	pro	IA HA vs. NSAIDs, IA CSs, IA PRP, or IA placebo; The current highest level of evidence suggests that IA HA is a viable option for knee OA.
2015 [41]	Meta-analysis	pro	IA HA vs. IA placebo; IA HA is safe and efficacious through 26 weeks in patients with symptomatic knee OA.
2017 [42]	Systemic review	pro	statistically significant improvements in pain, function and stiffness up to 26 weeks were found with IA HA therapy compared with IA placebo or controls
2018 [43]	Meta-analysis	pro	IA-HA vs. IA CS Both HA and CS injections were effective therapies for patients with knee OA.
2019 [44]	Meta-analysis	pro	IA HA provides a moderate symptomatic benefit to knee OA patients and without major safety concerns
2019 [45]	Systemic review	pro	OARSI guideline (2019) In the absence of comorbidity, the recommendation level is 2, and in the presence of cardiovascular and gastrointestinal comorbidity, the recommendation level is 1B.
2019 [46]	Meta-analysis	pro	Efficacy of IA HA: early-moderate OA vs. end-stage OA Regardless of OA stage, IA HA provided significant pain relief compared to the saline group, but the level of pain relief was lower in end-stage OA patients.
2019 [47]	Systemic review	pro	ESCEO 2019 Weak recommendation to the use of IAHA in patients who have contraindications to NSAIDs, or if the patient is still symptomatic despite the use of NSAIDs.
2020 [48]	Meta-analysis	pro	Six months of treatment IA HA and the combination of IA HA and triamcinolone improve pain and/or physical function in patients suffering from knee OA.

Table 2. *Cont.*

Publication Year [Ref.]	Study Design	Pro/Cons	Result
2021 [6]	Systemic review	pro	The use of IA HA is suggested for refractory patients who do not respond to treatment with drugs such as NSAIDs and acetaminophen.
2021 [49]	Systemic review	pro	Even when not supported by high evidence consensus, intra-articular CS and HA injections have gained precise indications for symptomatic relief and clinical improvement in OA.
2021 [50]	Meta-analysis	pro	Hylan G-F 20 at both frequencies (either as single or 1–3 weekly injections) are efficacious and generally well tolerated for long-term use.
2021 [51]	Systemic review	pro	HA reported good outcomes both for pain reduction and functional improvement.
2021 [52]	Meta-analysis	pro	In the meta-analysis, support the appropriate use of steroids and HAs for patients with Knee OA. For pain relief and AE, steroids are most likely the best treatment, followed by HA
2012 [53]	Systemic review	cons	IA HA has fewer benefits and increases the risk of serious side effects.
2016 [54]	Meta-analysis	cons	IA HA vs. physical therapy; Physical therapy agents seemed to have greater effects than IA HA on disability and pain.
2017 [55]	Meta-analysis	cons	IA-saline injection yields a statistically and clinically meaningful improvement up to 6 months after the injection in patients with knee OA. placebo effect for IA saline injections affects outcomes during comparative studies for the IA HA group
2019 [56]	Systemic review	cons	IA HA and IA CS can provide meaningful benefits to an appreciable number of patients, emerging evidence indicates that the apparent effectiveness of these treatments is largely a result of placebo effect.

CS, corticosteroid; ESCEO, The European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases; OARSI, Osteoarthritis Research Society International; AE, adverse effect.

2.1. Guidelines for the Use of HA

Osteoarthritis Research Society International (OARSI) revised in 2019 reported that the use of IA HAs needed caution in patients with OA of the knee at the recommended level. In the absence of comorbidity, the recommendation level was level 2. In the presence of cardiovascular and gastrointestinal comorbidity, the recommendation level was level 1B. Level 1B is a level approved by more than 75% of experts and conditionally recommended by more than 50% of experts. Level 2 is a level approved by 60 to 74% of experts. Although this guideline mentioned that IA HA could bring pain relief for more than 12 weeks after treatment, it recommended only when all core treatment failed [48]. The European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis, and Musculoskeletal Diseases (ESCEO) also published a revised guideline in 2019 and recommended that IA HA could be used for NSAIDs contraindication or for those who had failure with the use of NSAIDs (weak recommendation) [51]. In addition, the American College of Rheumatology (ACR) recommended the use of IA HA when CS injections failed to reduce symptoms such as joint pain [57].

On the other hand, some guidelines do not recommend the use of IA HA in patients with OA. First, the American Academy of Orthopedic Surgeons (AAOS) published the Clinical Practice Guideline on Treatment of Osteoarthritis of the Knee (2nd edition) in 2013 strongly discouraged the use of IA HA [58]. In the New England Journal of Medicine (NEJM) published in 2021, there is insufficient evidence to support a meaningful effect of IA HA with many side effects such as injection site reaction and joint swelling [59]. However, the evidence was based on one meta-analysis paper published by Rutjes et al. [38].

2.2. Hyaluronic Acid Physiology

The clinical benefit of IA HA for knee OA is from two perspectives: mechanical viscous replenishment in the joint cavity and re-establishment of intra-articular HA homeostasis by inducing the production of endogenous HA [60,61]. As mentioned above, hyaluronic acid is a substance present in cartilage and synovial fluid with molecular weights ranging

from 6500 to 10,900 kDa [62]. During arthritis, endogenous HA present in cartilage and synovial fluid is broken down into substances of high molecular weight and low molecular weight (depolymerization). Consequently, viscoelastic properties of the synovial fluid are reduced. Therefore, when HA is injected from the outside, it acts as a lubricant instead of an endogenous HA with a lower molecular weight. In addition, it induces the relief of pain caused by degenerative arthritis through various mechanisms [63]. There is also a report showing that exogenous HA can affect joints by slowing the degradation rate of type II collagen in the joint cavity [64]. After administering HA and methylprednisolone acetate (MPA) three times, the cartilage was biopsied 6 months later and examined for articular surface morphology, territorial matrix, chondrocyte number, and ultrastructure. It has been reported that the HA group has a higher chondrocyte density than the MPA group with improved appearance of the regional matrix, reconstitution of the superficial layer, and catabolism of chondrocytes [65].

Mechanistically, HA is known to attenuate phagocytosis and decrease cyclic adenosine monophosphate, fibronectin, and prostaglandin associated with inflammatory responses [66]. GoldBerg et al. have reported that HA has disease-modifying activity in OA patients through these actions [67]. There is also a paper showing that IA administration in patients with knee OA can significantly reduce hydrogen peroxide and peroxide in synovial fluid and protect cartilage by inhibiting apoptosis caused by hydrogen peroxide in chondrocytes [68].

2.3. Hyaluronic Acid Contraindication and Adverse Effects

There is no absolute contraindication of intra-articular injection of HA other than acute inflammation in the joint cavity, although drug effect may be reduced in the following cases. It is prohibited for use in diseases such as extensive bone edema, bone fissure or stress necrosis on MRI, acute diseases such as gout [69], and scleroderma [70]. In addition, in unstable meniscal tear, ligament laxity, and limb malalignment, not only viscosupplement, but also treatment of the underlying disease should be performed. Radiologic chondrocalcinosis is not a contraindication to HA [69]. For severe OA, HA is not contraindication, but it is known to be ineffective [50]. Eymard et al. have reported that IA HA should be considered only in patients with low BMI and low radiologic severity because high BMI and radiologic severity significantly increase the risk of IA HA failure [71].

Many papers have mentioned adverse effects of HA. Some papers have reported serious complications such as septic arthritis after the use of HA [72]. However, most research articles report only minor side effects associated with the use of HA. The degree of side effects is not particularly high compared to CS [73].

2.4. Comparison of HA Products/HA Products Mixed with Other Substances

HA is produced as various drugs due to differences in source (animals using modified organisms, bacterial fermentation), average molecular weight (MW) (low MW HA~ high MW HA), MW distribution, molecular structure, crosslinking method, concentration, and complex formulations such as mannitol and CS. Initially, rooster crests were used as a source of HA. Recently, modified bacteria have been used as the source [24]. Several research papers have been published on whether there is a difference in the effect depending on the characteristics of HA. HA can also be classified as follows according to its MW: (1) low MW (500–730 kDa); (2) intermediate MW (800–2000 kDa); and (3) high MW (2000–6000 kDa), including cross-linked formulations of HA. One paper has compared Sinovial®, an intermediate MW HA, and Synvisc®, a high MW HA, and reported that they show similar efficacy and safety despite their difference in MW [74]. One paper comparing a cross-linked HA, Hylan, a medium MW HA (avian origin), and a low MW HA (bacterial origin) has reported that effects of the three groups are similar except that Hylan has a slightly higher adverse effect [75]. Altman et al. have compared products with average MW above 3000 kDa and below and found that HA with high molecular weight can provide more favorable efficacy and a lower rate of discontinuation due to

treatment-related side effects [76]. There is no significant difference in the effect between HA alone and HAnOX-M®, a combination of mannitol and HA. Both agents have good effects [24,77,78]. Oxygen free radical neutralization by mannitol can retard degradation of both linear and cross-linked HA in several in vitro models of oxidative stress [79]. Several studies have published the efficacy of CS and HA complex formulations. Zhang et al. have observed radiological and pathological differences by administering control, HA, dexamethasone, and HA to an OA rat model. The knee joint space gap was significantly wider in the HA group. Less osteophytosis was observed in the dexamethasone group. In addition, it was observed that cartilage lesion formation was attenuated in the group using HA. Proteoglycan staining was stronger in the group using dexamethasone [80]. Clinically, in a paper comparing HA, the same amount of HA + triamcinolone (TA) 18 mg (Cingal®), and a control group, the drug group showed a significant effect on pain and function up to 26 weeks compared to the control group. In addition, the Cingal® group was significantly superior to the HA alone group at weeks 1 and 3, although they showed a similar pattern from weeks 6 to 26 [81].

2.5. HA Administration Method (Frequency, Dose)

Initial HA is mostly administered based on five times (once per week). However, as more studies comparing effects according to the HA usage method are published, there are now more cases where three times (once per week) are the default. According to Stitik et al., in 24 studies of 2168 people, when hyalgan was injected once a week and when a 3-week course and a 5-week course were compared, there was no statistical difference in pain reduction between the two [82]. Another paper reported that a single injection of HA did not have a statistically significant effect compared to the saline group and that there was no significant difference in the case of 5 or more injections compared to the group injected less than 5 times. Therefore, they reported that 2 to 4 administrations of HA were the most effective [83].

Since 2004, high-dose single injection therapy has been proposed as an alternative to dispensing equal amounts of HA. It is economical by reducing the number of hospital visits and procedures with a single injection. It has the advantage of reducing risks such as side effects of the procedure. Suppan et al. have reported that when 5 mL of 1% sodium hyaluronate is administered in a single dose, there is no difference in terms of efficacy or side effects between the two groups (single dose vs. administration of 2.5 mL of the same product three times) [84]. As mentioned above, although there is still controversy about the use of HA for OA of the knee, since there are no major side effects, it is recommended to consider the use of IA HA in patients who are ineffective in palliative treatment or find it difficult to use oral drugs.

3. Cross-Linked Hyaluronic Acid

Cross-linked hyaluronic acid (CL HA) is a high MW HA made by chemically crosslinking natural HA. Not all high MW HAs are cross-linked, but most are cross-linked HAs. The structure of CL HA is as follows (Figure 2) [7]. Many papers have reported that high MW CL HA is more effective than low MW HA. It has been reported that one administration of high MW HA has a similar effect to three administrations of low MW [85,86]. However, due to the specificity of crosslinking, pathological development of granulomatous inflammation, a pseudoseptic response, is also known [75]. Although the number of cases reported for adverse events is higher with CL HA, such adverse events are not severe enough to require medical intervention [86].

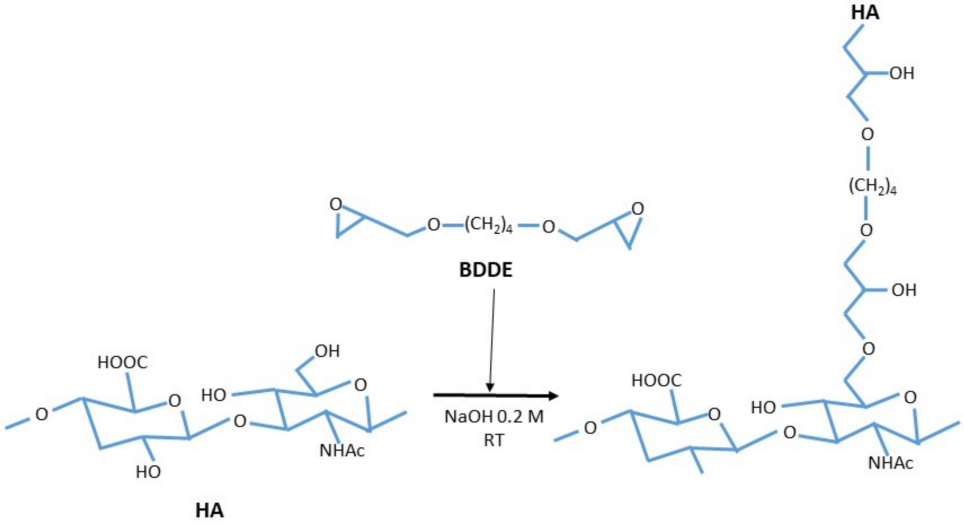


Figure 2. Traditional cross-linked transformation of HA with 1,4-butanediol diglycidyl ether (BDDE) [7].

Many studies have reported that CL HA is good for pain and knee function compared to the control group (saline). There are also papers on the effect and frequency of administration with general HA. Papers on how CL HA differs from regular HA are listed in Table 3. Table 3 summarizes 21 well-designed RCT papers among a total of 25 papers searched for IA CL HA. Seven papers have shown that it is effective for pain caused by OA of the knee compared to the saline group. There were two papers each comparing IA Steroid and oral administration of NSAIDs, and there was no significant difference in efficacy or better results. Another paper compared non-crosslinked HA and reported that a single administration of IA CL HA produced similar results to multiple administrations of IA HA.

Table 3. Clinical studies evaluating the efficacy of intra-articular cross-linked hyaluronic acid (CL HA) in knee osteoarthritis.

Publication Year	Study Design	Comparison Agent	Patients Number (Treat/Control)	Injection Times	Result
1995 [87]	RCT	NSAID	102(34/31/37)	3	Hylan G-F 20 was better than continuous NSAID therapy for VAS, joint function except activity restriction at 26 weeks
1998 [88]	RCT	saline	117(57/60)	3	VAS, pain during weight-bearing, resting, painful movement-dramatic improvement during 24 weeks
1999 [89]	RCT	LMW HA	70(38/32)	3	VAS, pain during weight-bearing, painful movement: Hylan G-F 20 patients significantly better results compare with LMW HA patients
2002 [90]	RCT	Artzal saline	210(70/70/70)	3	WOMAC, weight-bearing pain, resting pain, maximum pain: no significant differences in outcome between any of the three study groups during the first 26 weeks Significantly longer duration of clinical benefit for hyaluronan treatment than for placebo.
2003 [91]	RCT	betamethasone	100(50/50)	3	VAS, WOMAC improved: no significant differences in outcome between two group
2004 [92]	RCT	saline	346(172/174)	1	WOMAC and quality of life were improved in both; greater response to NASHA than placebo was observed at week 6
2004 [93]	RCT	TA	215(113/102)	3	WOMAC and VAS were improved in both; Hylan G-F 20 resulted in a longer duration of effect than TA
2005 [94]	RCT	HA	40(20/20)	3	Joint fluid aspiration: NO levels were reduced in both groups VAS, WOMAC improved: no significant differences in outcome between two group

Table 3. *Cont.*

Publication Year	Study Design	Comparison Agent	Patients Number (Treat/Control)	Injection Times	Result
2005 [95]	RCT	Orthovisc	184(92/92)	3	VAS, WOMAC improved during 52 weeks: no significant differences in outcome between two group
2007 [96]	RCT	MMW HA, LMW HA	660(220/220/220)	3	WOMAC improved: no significant differences in outcome between 3 group
2010 [97]	RCT	saline	232(115/117)	1	WOMAC and VAS were improved; Hylan G-F 20 statistically significantly greater improvements
2012 [98]	RCT	saline	379(251/128)	1	WOMAC and VAS were improved; GEL-200 statistically significantly greater improvements
2013 [99]	RCT	DCF, CN	61(20/21/20)	1	WOMAC improved: no significant differences in outcome between 3 group
2014 [100]	RCT	saline	218(108/110)	1	no significant differences in outcome; statistically significant improvement in pain relief at 6 weeks among patients without clinical effusion at baseline
2015 [101]	RCT	Artz	349(175/174)	1	Durolane 1 time vs. Artz 5 times WOMAC improved in both group; single injection of Durolane is non-inferior to 5 injections of Artz over 18 and 26 weeks for pain, physical function, global self-assessment, and knee stiffness
2018 [102]	RCT	Hylan G-F 20 (ADH)	258(129/129)	1	CCH vs. ADH VAS, WOMAC, Lequesne improved; CCH injection was superior to ADH injection.
2019 [103]	Open label, RCT	Usual care	156(77/79)	3	KOOS, VAS improved in both group; IA HMW-HA added to usual care is effective for knee OA in patients in the working age.
2019 [104]	RCT	saline	311(152/159)	1	WOMAC, VAS, stiffness improved; GEL-200 statistically significantly greater improvements
2019 [105]	Open label, prospective	non	46	2	decrease of cartilage catabolism, MRI cartilage volume and thickness increased
2019 [106]	RCT	saline	369(185/184)	1	WOMAC, VAS improved; Monovisc statistically significantly greater improvements
2020 [85]	RCT	Hyalgan	90(45/45)	3	WOMAC, VAS, LI improved in both group; Athromac statistically significantly greater improvements at WOMAC stiffness.

WOMAC, The Western Ontario and McMaster Universities Osteoarthritis Index; LI, Lequesne Index; OA, osteoarthritis; KOOS, knee injury and osteoarthritis outcome score; LMW, low molecular weight; MMW, medium molecular weight; DCF, diclofenac; CN, clodronate; *CCH*, chemically cross-linked hyaluronan; ADH, avian-derived hyaluronan.

3.1. Cross Linked Hyaluronic Acid Physiology

The background for the development of CL HA is that the half-life of HA injected to compensate for the decreased synovial HA concentration and chain length in OA patients is too short. It has been reported that unmodified low MW HA has a half-life of about 10 h, whereas CL HA can persist for an average of 8.8 ± 0.9 days [107]. The durability of the injection site is extended because the decomposition rate is slow while the elasticity and viscosity are increased [108].

3.2. Cross Linked HA Administration Method (Frequency, Dose)

In the initial paper announcing the efficacy of CL HA, CL HA was administered once a week for 3 weeks, just like natural HA [74,96,109]. However, in the case of CL HA, most papers have reported a similar effect to natural HA administered multiple times with one use [110,111]. In a paper, Hylan G-F 20, a CL HA, was administered at various doses and frequencies. It was found that a single administration of 6 mL of the drug was as effective as administration of 2 mL three times [112]. Although CL HA has been used clinically for a shorter period than HA, the basic structure of the two drugs is the same, and research results are continuously reported that even one administration of CL HA shows similar

effects to multiple administrations of HA. Therefore, it is recommended to consider the use of CL HA as well as HA in patients with OA of the knee.

4. Polynucleotide/Polydeoxyribonucleotide

Polynucleotide (PN) and polydeoxyribonucleotide (PDRN) are DNA fragments extracted from testis and semen of salmon or trout, respectively. As they are DNA polymers of testis and semen, they are substances widely used in regenerative medicine. PN and PDRN have been used for skin regeneration since the 1990s. They have been used for the treatment of osteoarthritis since the 2010s. Structure of PN and PDRN are shown as follows (Figure 3).

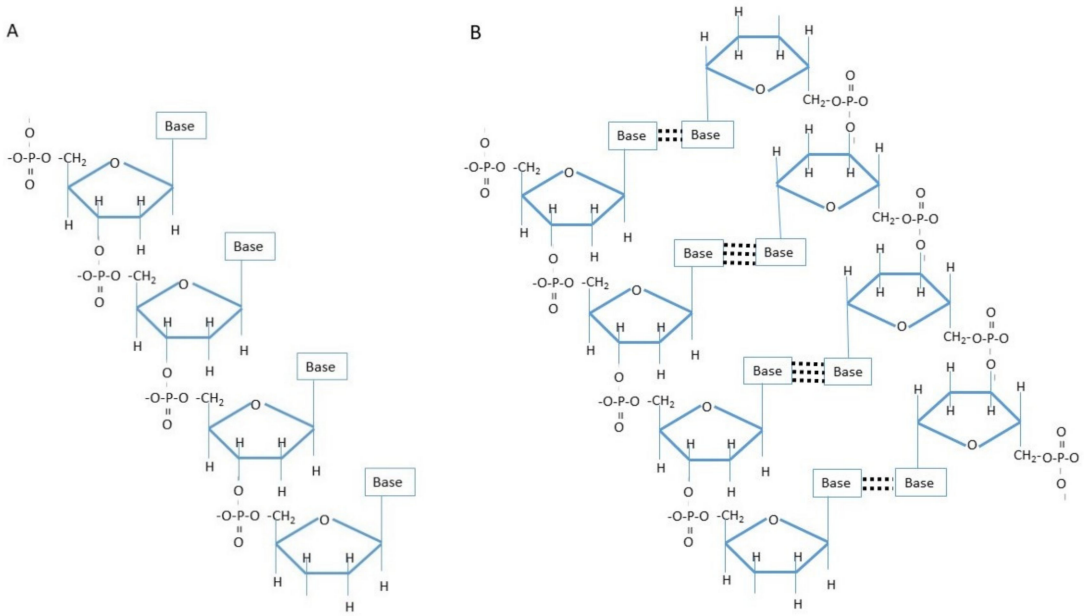


Figure 3. Structures of Polynucleotide (**A**) and Polydeoxyribonucleotide (**B**). Base = one of four bases of DNA.

PDRN is known to exert anti-inflammatory action without metabolic side effects, unlike NSAIDs or steroids. Because of this, it has been used to treat plantar fasciitis and supraspinatus tendinopathy patients in the pain area. It has been reported to be effective [113,114]. It is also effective for rheumatoid arthritis in animal models [115]. Yoon et al. have reported that, in patients with knee OA, compared to HA alone injection, combined administration of HA with PDRN has a statistically significant effect in VAS and WOMAC except for stiffness [116].

Like PDRN, PN is known to induce anti-inflammatory responses when administered in vivo [117]. Unlike PDRN, it is a substance with a high molecular weight that can bind to a large amount of water. Thus, it is a substance that can increase viscoelasticity. Several studies have demonstrated that these drugs are effective for OA of the knee. Related research articles are summarized in Table 4. Table 4 summarizes 6 papers on PN and 1 paper on PDRN in patients with osteoarthritis of the knee. As for the papers on PN, there were four RCTs, one open label study, and one retrospective observational study. Most of the papers showed similar or statistically significant improvement in pain control or functional improvement of knee arthritis compared to IA HA. Papers related to PDRN compared the IA HA alone group with the PDRN and HA combination group, and report that pain and function improved in the combined administration group.

Table 4. Clinical studies evaluating the efficacy of intra-articular PDRN/PN in knee osteoarthritis.

Publication Year [Ref]	Agent	Study Design	Comparison Agent	Patients Number (Treat/Control)	Injection Times	Result
2010 [118]	PN	RCT	HA	60(30/30)	5	VAS, KOOS, NSAID consumption improved: no significant differences in outcome between two group
2013 [119]	PN	Open label	non	95	Radiologic OA: 1 Severe OA: 3	KOOS, NRS, ROM improved.
2013 [120]	PN	RCT	HA	30(15/15)	3	VAS, KOOS improved in both group; PN statistically significantly greater improvements at KSS.
2013 [121]	PN	Retrospective	HA	60(30/30)	4	VAS, KOOS improved in both group; PN statistically significantly greater improvements after 6 month.
2014 [122]	PN	RCT	HA	72(36/36)	3	VAS, KOOS improved in both group; PN showed a significant difference after 2 weeks and HA after 18 weeks
2020 [123]	PN	RCT	HA	100(50/50)	3	PN + HA vs. HA VAS, KSS improved in both group: PN + HA group significantly greater improvements at knee function, pain.
2021 [124]	PN	Retrospective	HA, CLHA	15(5/5/5)	3	Function or weight-bearing pain, PN decreased the most by 6 weeks, and there was no difference between groups in VAS, K-WOMAC, EuroQoL, and painDETECT
2021 [125]	PN	RCT	HA	98(49/49)	3	PN + HA vs. HA WOMAC, KSS improved in both group: PN + HA group significantly greater improvements at knee function, pain after 2 years.
2019 [116]	PDRN	RCT	HA	30(15/15)	3	PDRN + HA vs. HA WOMAC, KSS improved in both group: PDRN + HA group significantly greater improvements at VAS, WOMAC.

PN, polynucleotide; PDRN, polydeoxyribonucleotide; K-WOMAC, Korean version of Western Ontario and McMaster Universities Osteoarthritis Index; KOOS, knee injury and osteoarthritis outcome score; ROM, range of motion; KSS, *Knee* Society clinical rating system.

4.1. PN/PDRN Physiology

The intra-articular use of PN serves to provide nutrients to restore the homeostasis of cartilage and environment within the joint. In addition, PN is a polymer material that combines with a large amount of water to form a three-dimensional gel. Because of these characteristics, when it is administered intra-articularly, pain caused by OA can be significantly reduced [122]. As is known, PN is physiologically present in the extracellular environment. It consists of simple nucleotides, nucleosides, and nitrogen bases that constitute the basic matrix of cells [126]. It also has the advantage of supporting the physiological repair process of cartilage by supplying these substrates to chondrocytes [122]. In addition, PN is a high-purity DNA polymer present in the human body. Thus, it has few side effects such as foreign body reaction [118]. It has been reported that PN is not toxic in chronic or acute toxicity studies [119]. As mentioned earlier, PDRN has anti-inflammatory properties. However, there are few clinical studies on it. Bitto et al. have reported that PDRN can affect levels of cytokines, particularly high mobility group box-1 (HMGB-1), tumor necrosis factor-α (TNF-α), interleukin (IL)-6, and IL-10 in human chondrocytes. In particular, upregulation of IL-10 suggests an anti-inflammatory action [115].

According to Baek et al., when a pro-inflammatory mediator was put into human chondrosarcoma cells to create a stress situation followed by treatment with PN and PDRN, they had a significant anti-inflammatory effect compared to the control group [117].

Although they are substances originated from regenerative medicine, there are no papers yet on the effect of PDRN or PN to regenerate chondrocytes in OA in vivo. It is

known that they have a protective effect on chondrocytes in vitro [127]. However, in an experiment in which PDRN was administered to a collagen-induced arthritis mice model, it was confirmed that the onset of arthritis was significantly attenuated compared to that in the control group [115].

4.2. PDRN/PN Administration Method (Frequency, Dose)

It has been reported that PN can be used in a 40 mg/2 mL prefilled syringe and PDRN can be used at 5.625 mg/3 mL (Placentex Inj®; Mastelli srl, Sanremo, Italy) [116,122]. The number of uses of PN or PDRN can be once a week to about 3–5 times, like HA [119,124,128]. PDRN/PN has recently been used in knee osteoarthritis compared to HA or CL HA. However, it has been used in the human body for a long time, has no major side effects, and has a large viscous replenishment effect. Therefore, it can be used in patients with knee osteoarthritis that is not suitable or effective for using HA or CL HA.

5. Conclusions

We summarized viscoelastic supplements used to treat knee OA. HA has been used in clinical practice for decades. However, even authoritative societies for arthritis report that its use is controversial. Although many papers have reported the effectiveness of hyaluronic acid in the management of osteoarthritis of the knee for pain reduction, the quality of the evidence is still insufficient. However, many studies have reported positive results regarding the efficacy of high (molecular weight) MW or (cross-linked hyaluronic acid) CL HA. In the case of PN and PDRN, there are not many published research papers since they are recently used for the treatment of osteoarthritis, although they are already widely used and clinically recognized. Thus, more studies with higher quality of evidence are needed in the future. However, as drugs that have been used for a long time without major side effects, HA and CL HA can be used in patients with osteoarthritis of the knee where there is no improvement in conservative management. The use of PDRN/PN may be a new option in patients who do not improve even after using HA and CL HA.

Author Contributions: Conceptualization, H.J.P. and J.J.; Methodology, H.J.P.; Software, investigation, M.C.R.; Resources, M.C.R.; Data curation; writing—original draft preparation, J.P.; Writing—review and editing, H.J.P.; Visualization, J.P.; Supervision H.J.P. and J.J.; Funding acquisition, none. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Castrogiovanni, P.; Trovato, F.M.; Loreto, C.; Nsir, H.; Szychlinska, M.A.; Musumeci, G. Nutraceutical supplements in the management and prevention of osteoarthritis. *Int. J. Mol. Sci.* **2016**, *17*, 2042. [CrossRef] [PubMed]
2. Barbour, K.; Helmick, C.; Boring, M.; Brady, T. Vital signs: Prevalence of doctor-diagnosed athritis and arthritis-attributable activity limitation—United States, 2013–2015. *MMWR Morb. Mortal Wkly. Rep.* **2017**, *66*, 246–253. [CrossRef]
3. Herrero-Beaumont, G.; Roman-Blas, J.A.; Bruyère, O.; Cooper, C.; Kanis, J.; Maggi, S.; Rizzoli, R.; Reginster, J.Y. Clinical settings in knee osteoarthritis: Pathophysiology guides treatment. *Maturitas* **2017**, *96*, 54–57. [CrossRef] [PubMed]
4. Zhang, W.; Moskowitz, R.W.; Nuki, G.; Abramson, S.; Altman, R.D.; Arden, N.; Bierma-Zeinstra, S.; Brandt, K.D.; Croft, P.; Doherty, M.; et al. OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. *Osteoarthr. Cartil.* **2008**, *16*, 137–162. [CrossRef] [PubMed]
5. Brosseau, L.; Taki, J.; Desjardins, B.; Thevenot, O.; Fransen, M.; Wells, G.A.; Mizusaki Imoto, A.; Toupin-April, K.; Westby, M.; Álvarez Gallardo, I.C.; et al. The Ottawa panel clinical practice guidelines for the management of knee osteoarthritis. Part two: Strengthening exercise programs. *Clin. Rehabil.* **2017**, *31*, 596–611. [CrossRef] [PubMed]
6. Testa, G.; Giardina, S.M.C.; Culmone, A.; Vescio, A.; Turchetta, M.; Cannavò, S.; Pavone, V. Intra-Articular Injections in Knee Osteoarthritis: A Review of Literature. *J. Funct. Morphol. Kinesiol.* **2021**, *6*, 15. [CrossRef]

7. López-Ruiz, E.; Jiménez, G.; Álvarez de Cienfuegos, L.; Antic, C.; Sabata, R.; Marchal, J.A.; Gálvez-Martín, P. Advances of hyaluronic acid in stem cell therapy and tissue engineering, including current clinical trials. *Eur. Cell Mater.* **2019**, *37*, 186–213. [CrossRef] [PubMed]
8. Grecomoro, G.; Martorana, U.; Di Marco, C. Intra-articular treatment with sodium hyaluronate in gonarthrosis: A controlled clinical trial versus placebo. *Pharmatherapeutica* **1987**, *5*, 137–141. [PubMed]
9. Leardini, G.; Mattara, L.; Franceschini, M.; Perbellini, A. Intra-articular treatment of knee osteoarthritis. A comparative study between hyaluronic acid and 6-methyl prednisolone acetate. *Clin. Exp. Rheumatol.* **1991**, *9*, 375–381. [PubMed]
10. Puhl, W.; Bernau, A.; Greiling, H.; Köpcke, W.; Pförringer, W.; Steck, K.J.; Zacher, J.; Scharf, H.P. Intra-articular sodium hyaluronate in osteoarthritis of the knee: A multicenter, double-blind study. *Osteoarthr. Cartil.* **1993**, *1*, 233–241. [CrossRef]
11. Henderson, E.B.; Smith, E.C.; Pegley, F.; Blake, D.R. Intra-articular injections of 750 kD hyaluronan in the treatment of osteoarthritis: A randomised single centre double-blind placebo-controlled trial of 91 patients demonstrating lack of efficacy. *Ann. Rheum. Dis.* **1994**, *53*, 529–534. [CrossRef] [PubMed]
12. Jones, A.C.; Pattrick, M.; Doherty, S.; Doherty, M. Intra-articular hyaluronic acid compared to intra-articular triamcinolone hexacetonide in inflammatory knee osteoarthritis. *Osteoarthr. Cartil.* **1995**, *3*, 269–273. [CrossRef]
13. Lohmander, L.S.; Dalén, N.; Englund, G.; Hämäläinen, M.; Jensen, E.M.; Karlsson, K.; Odensten, M.; Ryd, L.; Sernbo, I.; Suomalainen, O.; et al. Intra-articular hyaluronan injections in the treatment of osteoarthritis of the knee: A randomised, double blind, placebo controlled multicentre trial. Hyaluronan Multicentre Trial Group. *Ann. Rheum. Dis.* **1996**, *55*, 424–431. [CrossRef] [PubMed]
14. Altman, R.D.; Moskowitz, R. Intraarticular sodium hyaluronate (Hyalgan) in the treatment of patients with osteoarthritis of the knee: A randomized clinical trial. Hyalgan Study Group. *J. Rheumatol.* **1998**, *25*, 2203–2212.
15. Huskisson, E.C.; Donnelly, S. Hyaluronic acid in the treatment of osteoarthritis of the knee. *Rheumatology* **1999**, *38*, 602–607. [CrossRef] [PubMed]
16. Brandt, K.D.; Block, J.A.; Michalski, J.P.; Moreland, L.W.; Caldwell, J.R.; Lavin, P.T. Efficacy and safety of intraarticular sodium hyaluronate in knee osteoarthritis. ORTHOVISC Study Group. *Clin. Orthop. Relat. Res.* **2001**, *385*, 130–143. [CrossRef]
17. Petrella, R.J.; DiSilvestro, M.D.; Hildebrand, C. Effects of hyaluronate sodium on pain and physical functioning in osteoarthritis of the knee: A randomized, double-blind, placebo-controlled clinical trial. *Arch. Intern. Med.* **2002**, *162*, 292–298. [CrossRef] [PubMed]
18. Jubb, R.W.; Piva, S.; Beinat, L.; Dacre, J.; Gishen, P. A one-year, randomised, placebo (saline) controlled clinical trial of 500–730 kDa sodium hyaluronate (Hyalgan) on the radiological change in osteoarthritis of the knee. *Int. J. Clin. Pract.* **2003**, *57*, 467–474.
19. Day, R.; Brooks, P.; Conaghan, P.G.; Petersen, M. A double blind, randomized, multicenter, parallel group study of the effectiveness and tolerance of intraarticular hyaluronan in osteoarthritis of the knee. *J. Rheumatol.* **2004**, *31*, 775–782. [PubMed]
20. Neustadt, D.; Caldwell, J.; Bell, M.; Wade, J.; Gimbel, J. Clinical effects of intraarticular injection of high molecular weight hyaluronan (Orthovisc) in osteoarthritis of the knee: A randomized, controlled, multicenter trial. *J. Rheumatol.* **2005**, *32*, 1928–1936. [PubMed]
21. Petrella, R.J.; Petrella, M. A prospective, randomized, double-blind, placebo controlled study to evaluate the efficacy of intraarticular hyaluronic acid for osteoarthritis of the knee. *J. Rheumatol.* **2006**, *33*, 951–956. [PubMed]
22. Stitik, T.P.; Blacksin, M.F.; Stiskal, D.M.; Kim, J.H.; Foye, P.M.; Schoenherr, L.; Choi, E.S.; Chen, B.; Saunders, H.J.; Nadler, S.F. Efficacy and safety of hyaluronan treatment in combination therapy with home exercise for knee osteoarthritis pain. *Arch. Phys. Med. Rehabil.* **2007**, *88*, 135–141. [CrossRef] [PubMed]
23. Kalman, D.S.; Heimer, M.; Valdeon, A.; Schwartz, H.; Sheldon, E. Effect of a natural extract of chicken combs with a high content of hyaluronic acid (Hyal-Joint) on pain relief and quality of life in subjects with knee osteoarthritis: A pilot randomized double-blind placebo-controlled trial. *Nutr. J.* **2008**, *7*, 1–9. [CrossRef]
24. Altman, R.D.; Rosen, J.E.; Bloch, D.A.; Hatoum, H.T.; Korner, P. A double-blind, randomized, saline-controlled study of the efficacy and safety of EUFLEXXA for treatment of painful osteoarthritis of the knee, with an open-label safety extension (the FLEXX trial). *Semin. Arthritis Rheum.* **2009**, *39*, 1–9. [CrossRef]
25. Jørgensen, A.; Stengaard-Pedersen, K.; Simonsen, O.; Pfeiffer-Jensen, M.; Eriksen, C.; Bliddal, H.; Pedersen, N.W.; Bødtker, S.; Hørslev-Petersen, K.; Snerum, L.Ø.; et al. Intra-articular hyaluronan is without clinical effect in knee osteoarthritis: A multicentre, randomised, placebo-controlled, double-blind study of 337 patients followed for 1 year. *Ann. Rheum Dis.* **2010**, *69*, 1097–1102. [CrossRef] [PubMed]
26. Shimizu, M.; Higuchi, H.; Takagishi, K.; Shinozaki, T.; Kobayashi, T. Clinical and biochemical characteristics after intra-articular injection for the treatment of osteoarthritis of the knee: Prospective randomized study of sodium hyaluronate and corticosteroid. *Orthop. Sci.* **2010**, *15*, 51–56. [CrossRef]
27. Navarro-Sarabia, F.; Coronel, P.; Collantes, E.; Navarro, F.J.; de la Serna, A.R.; Naranjo, A.; Gimeno, M.; Herrero-Beaumont, G.; AMELIA study group. A 40-month multicentre, randomised placebo-controlled study to assess the efficacy and carry-over effect of repeated intra-articular injections of hyaluronic acid in knee osteoarthritis: The AMELIA project. *Ann. Rheum. Dis.* **2011**, *70*, 1957–1962. [CrossRef] [PubMed]
28. Huang, T.L.; Chang, C.C.; Lee, C.H.; Chen, S.C.; Lai, C.H.; Tsai, C.L. Intra-articular injections of sodium hyaluronate (Hyalgan) in osteoarthritis of the knee. a randomized, controlled, double-blind, multicenter trial in the Asian population. *BMC Musculoskelet Disord.* **2011**, *12*, 221. [CrossRef] [PubMed]

29. DeCaria, J.E.; Montero-Odasso, M.; Wolfe, D.; Chesworth, B.; Petrella, R.J. The effect of intra-articular hyaluronic acid treatment on gait velocity in older knee osteoarthritis patients: A randomized, controlled study. *Arch. Gerontol. Geriatr.* **2012**, *55*, 310–315. [CrossRef] [PubMed]
30. Housman, L.; Arden, N.; Schnitzer, T.J.; Birbara, C.; Conrozier, T.; Skrepnik, N.; Wei, N.; Bockow, B.; Waddell, D.; Tahir, H.; et al. Intra-articular hylastan versus steroid for knee osteoarthritis. *Knee Surg. Sports Traumatol. Arthrosc.* **2014**, *22*, 1684–1692. [CrossRef]
31. Ishijima, M.; Nakamura, T.; Shimizu, K.; Hayashi, K.; Kikuchi, H.; Soen, S.; Omori, G.; Yamashita, T.; Uchio, Y.; Chiba, J.; et al. Research Group of Cartilage Metabolism. Intra-articular hyaluronic acid injection versus oral non-steroidal anti-inflammatory drug for the treatment of knee osteoarthritis: A multi-center, randomized, open-label, non-inferiority trial. *Arthritis Res. Ther.* **2014**, *16*, R18. [CrossRef] [PubMed]
32. van der Weegen, W.; Wullems, J.A.; Bos, E.; Noten, H.; van Drumpt, R.A. No difference between intra-articular injection of hyaluronic acid and placebo for mild to moderate knee osteoarthritis: A randomized, controlled, double-blind trial. *J. Arthroplasty* **2015**, *30*, 754–757. [CrossRef] [PubMed]
33. Maia, P.A.V.; Cossich, V.R.A.; Salles-Neto, J.I.; Aguiar, D.P.; de Sousa, E.B. Viscosupplementation improves pain, function and muscle strength, but not proprioception, in patients with knee osteoarthritis: A prospective randomized trial. *Clinics* **2019**, *74*, e1207. [CrossRef]
34. Altman, R.D.; Devji, T.; Bhandari, M.; Fierlinger, A.; Niazi, F.; Christensen, R. Clinical benefit of intra-articular saline as a comparator in clinical trials of knee osteoarthritis treatments: A systematic review and meta-analysis of randomized trials. *Semin Arthritis Rheum.* **2016**, *46*, 151–159. [CrossRef] [PubMed]
35. Bellamy, N.; Campbell, J.; Robinson, V.; Gee, T.; Bourne, R.; Wells, G. Viscosupplementation for the treatment of osteoarthritis of the knee. *Cochrane Database Syst. Rev.* **2006**, *2*, CD005321. [CrossRef]
36. Zhang, W.; Nuki, G.; Moskowitz, R.W.; Abramson, S.; Altman, R.D.; Arden, N.K.; Bierma-Zeinstra, S.; Brandt, K.D.; Croft, P.; Doherty, M.; 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. *Osteoarthr. Cartil.* **2010**, *18*, 476–499. [CrossRef] [PubMed]
37. Bannuru, R.R.; Natov, N.S.; Dasi, U.R.; Schmid, C.H.; McAlindon, T.E. Therapeutic trajectory following intra-articular hyaluronic acid injection in knee osteoarthritis-meta-analysis. *Osteoarthr. Cartil.* **2011**, *19*, 611–619. [CrossRef] [PubMed]
38. Bannuru, R.R.; Schmid, C.H.; Kent, D.M.; Vaysbrot, E.E.; Wong, J.B.; McAlindon, T.E. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis: A systematic review and network meta-analysis. *Ann. Intern. Med.* **2015**, *162*, 46–54. [CrossRef] [PubMed]
39. Bruyere, O.; Cooper, C.; Pelletier, J.P.; Maheu, E.; Rannou, F.; Branco, J.; Luisa Brandi, M.; Kanis, J.A.; Altman, R.D.; Hochberg, M.C.; et al. A consensus statement on the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) algorithm for the management of knee osteoarthritis-From evidence-based medicine to the real-life setting. *Semin. Arthritis Rheum.* **2016**, *45*, S3–S11. [CrossRef]
40. Campbell, K.A.; Erickson, B.J.; Saltzman, B.M.; Mascarenhas, R.; Bach, B.R., Jr.; Cole, B.J.; Verma, N.N. Is Local Viscosupplementation Injection Clinically Superior to Other Therapies in the Treatment of Osteoarthritis of the Knee: A Systematic Review of Overlapping Meta-analyses. *Arthroscopy* **2015**, *31*, 2036–2045. [CrossRef]
41. Strand, V.; McIntyre, L.F.; Beach, W.R.; Miller, L.E.; Block, J.E. Safety and efficacy of US-approved viscosupplements for knee osteoarthritis: A systematic review and meta-analysis of randomized, saline-controlled trials. *J. Pain Res.* **2015**, *8*, 217–228. [PubMed]
42. Bhandari, M.; Bannuru, R.R.; Babins, E.M.; Martel-Pelletier, J.; Khan, M.; Raynauld, J.P.; Frankovich, R.; Mcleod, D.; Devji, T.; Phillips, M.; et al. Intra-articular hyaluronic acid in the treatment of knee osteoarthritis: A Canadian evidence-based perspective. *Ther. Adv. Musculoskelet Dis.* **2017**, *9*, 231–246. [CrossRef] [PubMed]
43. Ran, J.; Yang, X.; Ren, Z.; Wang, J.; Dong, H. Comparison of intra-articular hyaluronic acid and methylprednisolone for pain management in knee osteoarthritis: A meta-analysis of randomized controlled trials. *Int. J. Surg.* **2018**, *53*, 103–110. [CrossRef] [PubMed]
44. Maheu, E.; Bannuru, R.R.; Herrero-Beaumont, G.; Allali, F.; Bard, H.; Migliore, A. Why we should definitely include intra-articular hyaluronic acid as a therapeutic option in the management of knee osteoarthritis: Results of an extensive critical literature review. *Semin. Arthritis Rheum.* **2019**, *48*, 563–572. [CrossRef] [PubMed]
45. Bannuru, R.R.; Osani, M.C.; Vaysbrot, E.E.; Arden, N.K.; Bennell, K. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. *Osteoarthr. Cartil.* **2019**, *27*, 1578–1589. [CrossRef]
46. Nicholls, M.; Shaw, P.; Niazi, F.; Bhandari, M.; Bedi, A. The Impact of Excluding Patients with End-Stage Knee Disease in Intra-Articular Hyaluronic Acid Trials: A Systematic Review and Meta-Analysis. *Adv. Ther.* **2019**, *36*, 147–161. [CrossRef]
47. Bruyère, O.; Honvo, G.; Veronese, N.; Arden, N.K.; Branco, J.; Curtis, E.M.; Al-Daghri, N.M.; Herrero-Beaumont, G.; Martel-Pelletier, J.; Pelletier, J.P.; et al. An updated algorithm recommendation for the management of knee osteoarthritis from the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO). *Semin. Arthritis Rheum.* **2019**, *49*, 337–350. [CrossRef]

48. Beaudart, C.; Lengelé, L.; Leclercq, V.; Geerinck, A.; Sanchez-Rodriguez, D.; Bruyère, O.; Reginster, J.Y. Symptomatic Efficacy of Pharmacological Treatments for Knee Osteoarthritis: A Systematic Review and a Network Meta-Analysis with a 6-Month Time Horizon. *Drugs* **2020**, *80*, 1947–1959. [CrossRef] [PubMed]
49. Fusco, G.; Gambaro, F.M.; Di Matteo, B.; Kon, E. Injections in the osteoarthritic knee: A review of current treatment options. *EFORT Open Rev.* **2021**, *6*, 501–509. [CrossRef]
50. De Lucia, O.; Jerosch, J.; Yoon, S.; Sayre, T.; Ngai, W.; Filippou, G. One-year efficacy and safety of single or one to three weekly injections of hylan G-F 20 for knee osteoarthritis: A systematic literature review and meta-analysis. *Clin. Rheumatol.* **2021**, *40*, 2133–2142. [CrossRef]
51. Pavone, V.; Vescio, A.; Turchetta, M.; Giardina, S.M.C.; Culmone, A.; Testa, G. Injection-Based Management of Osteoarthritis of the Knee: A Systematic Review of Guidelines. *Front. Pharmacol.* **2021**, *20*, 661805. [CrossRef] [PubMed]
52. Han, S.B.; Seo, I.W.; Shin, Y.S. Intra-Articular Injections of Hyaluronic Acid or Steroids Associated with Better Outcomes Than Platelet-Rich Plasma, Adipose Mesenchymal Stromal Cells, or Placebo in Knee Osteoarthritis: A Network Meta-analysis. *Arthroscopy* **2021**, *37*, 292–306. [CrossRef]
53. Rutjes, A.W.; Jüni, P.; da Costa, B.R.; Trelle, S.; Nüesch, E.; Reichenbach, S. Viscosupplementation for osteoarthritis of the knee: A systematic review and meta-analysis. *Ann. Intern. Med.* **2012**, *157*, 180–191. [CrossRef]
54. Monticone, M.; Frizziero, A.; Rovere, G.; Vittadini, F.; Uliano, D.; LABruna, S.; Gatto, R.; Nava, C.; Leggero, V.; Masiero, S. Hyaluronic acid intra-articular injection and exercise therapy: Effects on pain and disability in subjects affected by lower limb joints osteoarthritis. A systematic review by the Italian Society of Physical and Rehabilitation Medicine (SIMFER). *Eur J. Phys. Rehabil Med.* **2016**, *52*, 389–399. [PubMed]
55. Saltzman, B.M.; Leroux, T.; Meyer, M.A.; Basques, B.A.; Chahal, J.; Bach, B.R.J.R.; Yanke, A.B.; Cole, B.J. The Therapeutic Effect of Intra-articular Normal Saline Injections for Knee Osteoarthritis: A Meta-analysis of Evidence Level 1 Studies. *Am. J. Sports Med.* **2017**, *45*, 2647–2653. [CrossRef]
56. Jones, I.A.; Togashi, R.; Wilson, M.L.; Heckmann, N.; Vangsness, C.T., Jr. Intra-articular treatment options for knee osteoarthritis. *Nat. Rev. Rheumatol.* **2019**, *15*, 77–90. [CrossRef] [PubMed]
57. Kolasinski, S.L.; Neogi, T.; Hochberg, M.C.; Oatis, C.; Guyatt, G.; Block, J.; Callahan, L.; Copenhaver, C.; Dodge, C.; Felson, D.; et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. *Arthritis Care Res.* **2020**, *72*, 149–162. [CrossRef] [PubMed]
58. Brown, G.A. AAOS clinical practice guideline: Treatment of osteoarthritis of the knee: Evidence-based guideline, 2nd edition. *J. Am. Acad. Orthop. Surg.* **2013**, *21*, 577–579. [PubMed]
59. Sharma, L. Osteoarthritis of the Knee. *N. Engl. J. Med.* **2021**, *384*, 51–59. [CrossRef]
60. Maheu, E.; Rannou, F.; Reginster, J.Y. Efficacy and safety of hyaluronic acid in the management of osteoarthritis: Evidence from real-life setting trials and surveys. *Semin. Arthritis Rheum.* **2016**, *45*, S28–S33. [CrossRef] [PubMed]
61. Nguyen, C.; Lefèvre-Colau, M.M.; Poiraudeau, S.; Rannou, F. Evidence and recommendations for use of intra-articular injections for knee osteoarthritis. *Ann. Phys. Rehabil. Med.* **2016**, *59*, 184–189. [CrossRef]
62. Bowman, S.; Awad, M.E.; Hamrick, M.W.; Hunter, M.; Fulzele, S. Recent advances in hyaluronic acid based therapy for osteoarthritis. *Clin. Transl. Med.* **2018**, *7*, 6. [CrossRef]
63. Stern, R.; Jedrzejas, M.J. Hyaluronidases: Their genomics, structures, and mechanisms of action. *Chem. Rev.* **2006**, *106*, 818–839. [CrossRef] [PubMed]
64. Conrozier, T.; Balblanc, J.C.; Richette, P.; Mulleman, D.; Maillet, B.; Henrotin, Y.; Rannou, F.; Piroth, C.; Hilliquin, P.; Mathieu, P.; et al. Osteoarthritis Group of the French Society of Rheumatology. Early effect of hyaluronic acid intra-articular injections on serum and urine biomarkers in patients with knee osteoarthritis: An open-label observational prospective study. *J. Orthop. Res.* **2012**, *30*, 679–685. [CrossRef]
65. Guidolin, D.D.; Ronchetti, I.P.; Lini, E.; Guerra, D.; Frizziero, L. Morphological analysis of articular cartilage biopsies from a randomized, clinical study comparing the effects of 500–730 kDa sodium hyaluronate (Hyalgan) and methylprednisolone acetate on primary osteoarthritis of the knee. *Osteoarthr. Cartil.* **2001**, *9*, 371–381. [CrossRef] [PubMed]
66. Bert, J.M.; Bert, T.M. Nonoperative treatment of unicompartmental arthritis: From bracing to injection. *Clin. Sports Med.* **2014**, *33*, 1–10. [CrossRef] [PubMed]
67. Goldberg, V.M.; Goldberg, L. Intra-articular hyaluronans: The treatment of knee pain in osteoarthritis. *J. Pain Res.* **2010**, *3*, 51–56. [CrossRef] [PubMed]
68. Khalaj, N.; Abu Osman, N.A.; Mokhtar, A.H.; George, J.; Abas, W.A. Effect of intra-articular hyaluronic injection on postural stability and risk of fall in patients with bilateral knee osteoarthritis. *Sci. World J.* **2014**, *2014*, 815184. [CrossRef] [PubMed]
69. Legré-Boyer, V. Viscosupplementation: Techniques, indications, results. *Orthop. Traumatol. Surg. Res.* **2015**, *101*, S101–S108. [CrossRef] [PubMed]
70. Gualdi, G.; Monari, P.; Cammalleri, D.; Pelizzari, L.; Calzavara-Pinton, P. Hyaluronic acid-based products are strictly contraindicated in scleroderma-related skin ulcers. *Wounds* **2019**, *31*, 81–88.
71. Eymard, F.; Chevalier, X.; Conrozier, T. Obesity and radiological severity are associated with viscosupplementation failure in patients with knee osteoarthritis. *J. Orthop. Res.* **2017**, *35*, 2269–2274. [CrossRef]
72. So, K.Y.; Lee, H.Y. Septic Arthritis after Intra-articular Hyaluronic Acid Injections in Patients with Knee Osteoarthritis-A report of two cases. *Korean J. Pain.* **2002**, *15*, 80–83.

73. He, W.W.; Kuang, M.J.; Zhao, J.; Sun, L.; Lu, B.; Wang, Y.; Ma, J.X.; Ma, X.L. Efficacy and safety of intraarticular hyaluronic acid and corticosteroid for knee osteoarthritis: A meta-analysis. *Int. J. Surg.* **2017**, *39*, 95–103. [CrossRef] [PubMed]
74. Pavelka, K.; Uebelhart, D. Efficacy evaluation of highly purified intra-articular hyaluronic acid (Sinovial(®)) vs hylan G-F20 (Synvisc(®)) in the treatment of symptomatic knee osteoarthritis. A double-blind, controlled, randomized, parallel-group non-inferiority study. *Osteoarthr. Cartil.* **2011**, *19*, 1294–1300. [CrossRef] [PubMed]
75. Yoshioka, K.; Katayama, M.; Nishiyama, T.; Harada, K.; Takeshita, S.; Kawamata, Y. Biocompatibility study of different hyaluronan products for intra-articular treatment of knee osteoarthritis. *BMC Musculoskelet Disord.* **2019**, *20*, 424. [CrossRef]
76. Altman, R.D.; Bedi, A.; Karlsson, J.; Sancheti, P.; Schemitsch, E. Product Differences in Intra-articular Hyaluronic Acids for Osteoarthritis of the Knee. *Am. J. Sports Med.* **2016**, *44*, 2158–2165. [CrossRef]
77. Conrozier, T.; Eymard, F.; Afif, N.; Balblanc, J.C.; Legré-Boyer, V.; Chevalier, X.; Happyvisc Study Group. Safety and efficacy of intra-articular injections of a combination of hyaluronic acid and mannitol (HAnOX-M) in patients with symptomatic knee osteoarthritis: Results of a double-blind, controlled, multicenter, randomized trial. *Knee* **2016**, *23*, 842–848. [CrossRef]
78. Borrás-Verdera, A.; Calcedo-Bernal, V.; Ojeda-Levenfeld, J.; Clavel-Sainz, C. Efficacy and safety of a single intra-articular injection of 2% hyaluronic acid plus mannitol in knee osteoarthritis over a 6-month period. *Rev. Esp. Cir. Ortop. Traumatol.* **2012**, *56*, 274–280. [CrossRef] [PubMed]
79. Conrozier, T. Is the Addition of a Polyol to Hyaluronic Acid a Significant Advance in the Treatment of Osteoarthritis? *Curr. Rheumatol. Rev.* **2018**, *14*, 226–230. [CrossRef]
80. Zhang, Z.; Wei, X.; Gao, J.; Zhao, Y.; Zhao, Y.; Guo, L.; Chen, C.; Duan, Z.; Li, P.; Wei, L. Intra-Articular Injection of Cross-Linked Hyaluronic Acid-Dexamethasone Hydrogel Attenuates Osteoarthritis: An Experimental Study in a Rat Model of Osteoarthritis. *Int. J. Mol. Sci.* **2016**, *17*, 411. [CrossRef]
81. Hangody, L.; Szody, R.; Lukasik, P.; Zgadzaj, W.; Lénárt, E.; Dokoupilova, E.; Bichovsk, D.; Berta, A.; Vasarhelyi, G.; Ficzere, A.; et al. Intraarticular Injection of a Cross-Linked Sodium Hyaluronate Combined with Triamcinolone Hexacetonide (Cingal) to Provide Symptomatic Relief of Osteoarthritis of the Knee: A Randomized, Double-Blind, Placebo-Controlled Multicenter Clinical Trial. *Cartilage* **2018**, *9*, 276–283. [CrossRef]
82. Stitik, T.P.; Issac, S.M.; Modi, S.; Nasir, S.; Kulinets, I. Effectiveness of 3 Weekly Injections Compared With 5 Weekly Injections of Intra-Articular Sodium Hyaluronate on Pain Relief of Knee Osteoarthritis or 3 Weekly Injections of Other Hyaluronan Products: A Systematic Review and Meta-Analysis. *Arch. Phys. Med. Rehabil.* **2017**, *98*, 1042–1050. [CrossRef]
83. Concoff, A.; Sancheti, P.; Niazi, F.; Shaw, P.; Rosen, J. The efficacy of multiple versus single hyaluronic acid injections: A systematic review and meta-analysis. *BMC Musculoskelet Disord.* **2017**, *18*, 542. [CrossRef]
84. Suppan, V.K.L.; Wei, C.Y.; Siong, T.C.; Mei, T.M.; Chern, W.B.; Nanta Kumar, V.K.; Sheng, K.R.; Sadashiva Rao, A. Randomized controlled trial comparing efficacy of conventional and new single larger dose of intra-articular viscosupplementation in management of knee osteoarthritis. *J. Orthop. Surg.* **2017**, *25*, 1–6. [CrossRef] [PubMed]
85. Bahrami, M.H.; Raeissadat, S.A.; Cheraghi, M.; Rahimi-Dehgolan, S.; Ebrahimpour, A. Efficacy of single high-molecular-weight versus triple low-molecular-weight hyaluronic acid intra-articular injection among knee osteoarthritis patients. *BMC Musculoskelet Disord.* **2020**, *21*, 550. [CrossRef] [PubMed]
86. Ha, C.W.; Park, Y.B.; Choi, C.H.; Kyung, H.S.; Lee, J.H.; Yoo, J.D.; Yoo, J.H.; Choi, C.H.; Kim, C.W.; Kim, H.C.; et al. Efficacy and safety of single injection of cross-linked sodium hyaluronate vs. three injections of high molecular weight sodium hyaluronate for osteoarthritis of the knee: A double-blind, randomized, multi-center, non-inferiority study. *BMC Musculoskelet Disord.* **2017**, *18*, 223. [CrossRef] [PubMed]
87. Adams, M.E.; Atkinson, M.H.; Lussier, A.J.; Schulz, J.I.; Siminovitch, K.A.; Wade, J.P.; Zummer, M. The role of viscosupplementation with hylan G-F 20 (Synvisc) in the treatment of osteoarthritis of the knee: A Canadian multicenter trial comparing hylan G-F 20 alone, hylan G-F 20 with non-steroidal anti-inflammatory drugs (NSAIDs) and NSAIDs alone. *Osteoarthr. Cartil.* **1995**, *3*, 213–225. [CrossRef]
88. Wobig, M.; Dickhut, A.; Maier, R.; Vetter, G. Viscosupplementation with hylan G-F 20: A 26-week controlled trial of efficacy and safety in the osteoarthritic knee. *Clin. Ther.* **1998**, *20*, 410–423. [CrossRef]
89. Wobig, M.; Bach, G.; Beks, P.; Dickhut, A.; Runzheimer, J.; Schwieger, G.; Vetter, G.; Balazs, E. The role of elastoviscosity in the efficacy of viscosupplementation for osteoarthritis of the knee: A comparison of hylan G-F 20 and a lower-molecular-weight hyaluronan. *Clin. Ther.* **1999**, *21*, 1549–1562. [CrossRef]
90. Karlsson, J.; Sjögren, L.S.; Lohmander, L.S. Comparison of two hyaluronan drugs and placebo in patients with knee osteoarthritis. A controlled, randomized, double-blind, parallel-design multicentre study. *Rheumatology* **2002**, *41*, 1240–1248. [CrossRef] [PubMed]
91. Leopold, S.S.; Redd, B.B.; Warme, W.J.; Wehrle, P.A.; Pettis, P.D.; Shott, S. Corticosteroid compared with hyaluronic acid injections for the treatment of osteoarthritis of the knee. A prospective, randomized trial. *J. Bone Joint Surg. Am.* **2003**, *85*, 1197–1203. [CrossRef] [PubMed]
92. Altman, R.D.; Akermark, C.; Beaulieu, A.D.; Schnitzer, T. Durolane International Study Group. Efficacy and safety of a single intra-articular injection of non-animal stabilized hyaluronic acid (NASHA) in patients with osteoarthritis of the knee. *Osteoarthr. Cartil.* **2004**, *12*, 642–649. [CrossRef] [PubMed]
93. Caborn, D.; Rush, J.; Lanzer, W.; Parenti, D.; Murray, C. A randomized, single-blind comparison of the efficacy and tolerability of hylan G-F 20 and triamcinolone hexacetonide in patients with osteoarthritis of the knee. *J. Rheumatol.* **2004**, *31*, 333–343. [PubMed]

94. Karatay, S.; Kiziltunc, A.; Yildirim, K.; Karanfil, R.C.; Senel, K. Effects of different hyaluronic acid products on synovial fluid NO levels in knee osteoarthritis. *Clin. Rheumatol.* **2005**, *24*, 497–501. [CrossRef]
95. Karatosun, V.; Unver, B.; Gocen, Z.; Sen, A. Comparison of two hyaluronan drugs in patients with advanced osteoarthritis of the knee. A prospective, randomized, double-blind study with long term follow-up. *Clin. Exp. Rheumatol.* **2005**, *23*, 213–218.
96. Jüni, P.; Reichenbach, S.; Trelle, S.; Tschannen, B.; Wandel, S.; Jordi, B.; Züllig, M.; Guetg, R.; Häuselmann, H.J.; Schwarz, H.; et al. Efficacy and safety of intraarticular hylan or hyaluronic acids for osteoarthritis of the knee: A randomized controlled trial. *Arthritis Rheum.* **2007**, *56*, 3610–3619. [CrossRef]
97. Chevalier, X.; Jerosch, J.; Goupille, P.; van Dijk, N.; Luyten, F.P.; Scott, D.L.; Bailleul, F.; Pavelka, K. Single, intra-articular treatment with 6 ml hylan G-F 20 in patients with symptomatic primary osteoarthritis of the knee: A randomised, multicentre, double-blind, placebo controlled trial. *Ann. Rheum. Dis.* **2010**, *69*, 113–119. [CrossRef] [PubMed]
98. Strand, V.; Baraf, H.S.B.; Lavin, P.T.; Lim, S.; Hosokawa, H. A multicenter, randomized controlled trial comparing a single intra-articular injection of Gel-200, a new cross-linked formulation of hyaluronic acid, to phosphate buffered saline for treatment of osteoarthritis of the knee. *Osteoarthr. Cartil.* **2012**, *20*, 350–356. [CrossRef] [PubMed]
99. Palmieri, B.; Rottigni, V.; Iannitti, T. Preliminary study of highly cross-linked hyaluronic acid-based combination therapy for management of knee osteoarthritis-related pain. *Drug Des. Devel Ther.* **2013**, *7*, 7–12.
100. Arden, N.K.; Åkermark, C.; Andersson, M.; Todman, M.G.; Altman, R.D. A randomized saline-controlled trial of NASHA hyaluronic acid for knee osteoarthritis. *Curr. Med. Res. Opin.* **2014**, *30*, 279–286. [CrossRef] [PubMed]
101. Zhang, H.; Zhang, K.; Zhang, X.; Zhu, Z.; Yan, S.; Sun, T.; Guo, A.; Jones, J.; Steen, R.G.; Shan, B.; et al. Comparison of two hyaluronic acid formulations for safety and efficacy (CHASE) study in knee osteoarthritis: A multicenter, randomized, double-blind, 26-week non-inferiority trial comparing Durolane to Artz. *Arthritis Res. Ther.* **2015**, *17*, 51. [CrossRef]
102. Guo, Y.; Yang, P.; Liu, L. Origin and Efficacy of Hyaluronan Injections in Knee Osteoarthritis: Randomized, Double-Blind Trial. *Med. Sci. Monit.* **2018**, *24*, 4728–4737. [CrossRef] [PubMed]
103. Hermans, J.; Bierma-Zeinstra, S.M.A.; Bos, P.K.; Niesten, D.D.; Verhaar, J.A.N.; Reijman, M. The effectiveness of high molecular weight hyaluronic acid for knee osteoarthritis in patients in the working age: A randomised controlled trial. *BMC Musculoskelet Disord.* **2019**, *20*, 196. [CrossRef] [PubMed]
104. Takamura, J.; Seo, T.; Strand, V. A Single Intra-Articular Injection of Gel-200 for Treatment of Symptomatic Osteoarthritis of the Knee Is More Effective than Phosphate Buffered Saline at 6 Months: A Subgroup Analysis of a Multicenter, Randomized Controlled Trial. *Cartilage* **2019**, *10*, 417–422. [CrossRef] [PubMed]
105. Henrotin, Y.; Bannuru, R.; Malaise, M.; Ea, H.K.; Confavreux, C.; Bentin, J.; Urbin-Choffray, D.; Conrozier, T.; Brasseur, J.P.; Thomas, P.; et al. Hyaluronan derivative HYMOVIS® increases cartilage volume and type ii collagen turnover in osteoarhritic knee: Data from MOKHA study. *BMC Musculoskelet Disord.* **2019**, *20*, 293. [CrossRef] [PubMed]
106. Petterson, S.C.; Plancher, K.D. Single intra-articular injection of lightly cross-linked hyaluronic acid reduces knee pain in symptomatic knee osteoarthritis: A multicenter, double-blind, randomized, placebo-controlled trial. *Knee Surg. Sports Traumatol. Arthrosc.* **2019**, *27*, 1992–2002. [CrossRef] [PubMed]
107. Larsen, N.E.; Dursema, H.D.; Pollak, C.T.; Skrabut, E.M. Clearance kinetics of a hylan-based viscosupplement after intra-articular and intravenous administration in animal models. *J. Biomed. Mater. Res. B Appl. Biomater.* **2012**, *100*, 457–462. [CrossRef] [PubMed]
108. Balazs, E.A.; Denlinger, J.L. Viscosupplementation: A new concept in the treatment of osteoarthritis. *J. Rheum. Suppl.* **1993**, *39*, 3–9.
109. Wang, Y.; Hall, S.; Hanna, F.; Wluka, A.E.; Grant, G.; Marks, P.; Feletar, M.; Cicuttini, F.M. Effects of Hylan G-F 20 supplementation on cartilage preservation detected by magnetic resonance imaging in osteoarthritis of the knee: A two-year single-blind clinical trial. *BMC Musculoskelet Disord.* **2011**, *12*, 195. [CrossRef]
110. Khanasuk, Y.; Dechmaneenin, T.; Tanavalee, A. Prospective randomized trial comparing the efficacy of single 6-ml injection of hylan G-F 20 and hyaluronic acid for primary knee arthritis: A preliminary study. *J. Med. Assoc. Thai.* **2012**, *95*, 92–97.
111. Frampton, J.E. Hylan G-F 20 single-injection formulation. *Drugs Aging* **2010**, *27*, 77–85. [CrossRef] [PubMed]
112. Conrozier, T.; Jerosch, J.; Beks, P.; Kemper, F.; Euller-Ziegler, L.; Bailleul, F.; Chevalier, X. Prospective, multi-centre, randomised evaluation of the safety and efficacy of five dosing regimens of viscosupplementation with hylan G-F 20 in patients with symptomatic tibio-femoral osteoarthritis: A pilot study. *Arch. Orthop Trauma Surg.* **2009**, *129*, 417–423. [CrossRef] [PubMed]
113. Kim, J.K.; Chung, J.Y. Effectiveness of polydeoxyribonucleotide injection versus normal saline injection for treatment of chronic plantar fasciitis: A prospective randomised clinical trial. *Int Orthop.* **2015**, *39*, 1329–1334. [CrossRef]
114. Yoon, Y.C.; Lee, D.H.; Lee, M.Y.; Yoon, S.H. Polydeoxyribonucleotide injection in the treatment of chronic supraspinatus tendinopathy: A case-controlled, retrospective, comparative study with 6-month follow-up. *Arch. Phys. Med. Rehabil.* **2017**, *98*, 874–880. [CrossRef] [PubMed]
115. Bitto, A.; Polito, F.; Irrera, N.; D'Ascola, A.; Avenoso, A.; Nastasi, G.; Campo, G.M.; Micali, A.; Bagnato, G.; Minutoli, L.; et al. Polydeoxyribonucleotide reduces cytokine production and the severity of collagen-induced arthritis by stimulation of adenosine $A(_2A)$ receptor. *Arthritis Rheum.* **2011**, *63*, 3364–3371. [CrossRef] [PubMed]
116. Yoon, S.; Kang, J.J.; Kim, J.; Park, S.; Kim, J.M. Efficacy and safety of intra-articular injections of hyaluronic acid combined with polydeoxyribonucleotide in the treatment of knee osteoarthritis. *Ann. Rehabil. Med.* **2019**, *43*, 204–214. [CrossRef] [PubMed]
117. Baek, A.; Kim, M.; Kim, S.H.; Cho, S.R.; Kim, H.J. Anti-inflammatory Effect of DNA Polymeric Molecules in a Cell Model of Osteoarthritis. *Inflammation* **2018**, *41*, 677–688. [CrossRef] [PubMed]

118. Vanelli, R.; Costa, P.; Rossi, S.M.P.; Benazzo, F. Efficacy of intra-articular polynucleotides in the treatment of knee osteoarthritis: A randomized, double-blind clinical trial. *Knee Surg. Sports Traumatol. Arthrosc.* **2010**, *18*, 901–907. [CrossRef] [PubMed]
119. Saggini, R.; Di Stefano, A.; Cavezza, T.; Saladino, G.; Bellomo, R. Intrarticular treatment of osteoartropaty knee with polynucleotides: A pilot study with medium-term follow-up. *J. Biol. Regul. Homeost. Agents* **2013**, *27*, 543–549. [PubMed]
120. Zazgyva, A.; Gergely, I.; Russu, O.M.; Roman, C.; Pop, T.S. Polynucleotides versus sodium hyaluronate in the local treatment of knee osteoarthritis. *Acta Med. Transilv.* **2013**, *2*, 260–263.
121. Meccariello, L.; Cioffi, S.; Franzese, R.; Cioffi, R.; Petrucci, C.; Errico, G.; Olivieri, M.; Mugnaini, M. Intraarticular knee joint injection: Hyaluronic acid vs polynucleotides. *Euromediterranean Biomed. J.* **2013**, *8*, 35–41.
122. Giarratana, L.S.; Marelli, B.M.; Crapanzano, C.; De Martinis, S.E.; Gala, L.; Ferraro, M.; Marelli, N.; Albisetti, W. A randomized double-blind clinical trial on the treatment of knee osteoarthritis: The efficacy of polynucleotides compared to standard hyaluronian viscosupplementation. *Knee* **2014**, *21*, 661–668. [CrossRef] [PubMed]
123. Dallari, D.; Sabbioni, G.; Del Piccolo, N.; Carubbi, C.; Veronesi, F.; Torricelli, P.; Fini, M. Efficacy of Intra-Articular Polynucleotides Associated with Hyaluronic Acid Versus Hyaluronic Acid Alone in the Treatment of Knee Osteoarthritis: A Randomized, Double-Blind, Controlled Clinical Trial. *Clin. J. Sport Med.* **2020**, *30*, 1–7. [CrossRef]
124. Kim, J.Y.; Kim, Y.N.; Lee, Y.J.; Sim, S.E.; Ko, Y.R.; Shim, J.W.; Lee, K.S.; Joo, M.; Park, H.J. Pilot Study to Evaluate the Efficacy of Polynucleotide Sodium Compared to Sodium Hyaluronate and Crosslinked Sodium Hyaluronate in Patients with Knee Osteoarthritis. *J. Clin. Med.* **2021**, *10*, 1138. [CrossRef]
125. Stagni, C.; Rocchi, M.; Mazzotta, A.; Piccolo, N.D.; Rani, N.; Govoni, M.; Vivarelli, L.; Veronesi, F.; Fini, M.; Dallari, D. Randomised, double-blind comparison of a fixed co-formulation of intra-articular polynucleotides and hyaluronic acid versus hyaluronic acid alone in the treatment of knee osteoarthritis: Two-year follow-up. *Res. Sq.* **2021**, *1*, 1–44. [CrossRef] [PubMed]
126. Rathbone, M.P.; Christjanson, L.; Deforge, S.; Deluca, B.; Gysbers, J.W.; Hindley, S.; Jovetich, M.; Middlemiss, P.; Takhal, S. Extracellular purine nucleosides stimulate cell division and morphogenesis: Pathological and physiological implications. *Med. Hypotheses* **1992**, *37*, 232–240. [CrossRef]
127. Gennero, L.; Denysenko, T.; Calisti, G.F.; Vercelli, A.; Vercelli, C.M.; Amedeo, S.; Mioletti, S.; Parino, E.; Montanaro, M.; Melcarne, A.; et al. Protective effects of polydeoxyribonucleotides on cartilage degradation in experimental cultures. *Cell Biochem. Funct.* **2013**, *31*, 214–227. [CrossRef] [PubMed]
128. Kim, M.S.; Cho, R.K.; In, Y. Zhang of polydeoxyribonucleotide for the treatment of knee osteoarthritis: Systematic review and meta-analysis of randomized controlled trials. *Medicine* **2019**, *98*, e17386. [CrossRef] [PubMed]