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EFFICACY AND SAFETY OF VISCOSUPLEMENTATION IN KNEE OSTEOARTHRITIS: A NARRATIVE REVIEW

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Abstract: OBJECTIVES: The objective of this study was to conduct a literature review on viscosupplementation, which consists of intra-articular therapy with hyaluronic acid, applied in patients with knee osteoarthritis. The goal was to build a robust scientific basis that would enable healthcare professionals to make positive decisions for their patients. The review addresses the effectiveness of viscosupplementation in analgesia, reduction of joint stiffness, and improvement of knee function. In addition, possible adverse effects related to the use of this therapy were discussed, aiming to provide a comprehensive and informed view of its applications and clinical implications. **MATERIALS AND METHODS:** To carry out this study, a literature search was conducted in the PUBMED database on July 12, 2024. The keywords "KNEE OSTEOARTHRITS," " VISCOSSUPLEMENTATION," and " INTRAARTICULAR" were used. HYALURONIC ACID, THERAPEUTICS. The search on PUBMED resulted in 125 articles, the abstracts of which were read, and the most recent articles published in the last ten years were selected, including articles in English, Spanish, and Polish, and excluding articles with conflicts of interest and articles that did not deal with the use of viscosupplementation in patients with knee osteoarthritis as the main subject of study. A total of 17 articles from the 125 found in the search were included in the final study. After the selection of the articles, four independent researchers read the texts in their entirety between August 2, 2024, and September 2, 2024. After reading the articles, the four researchers held three meetings between September 2, 2024, and October 2, 2024, during which they discussed the topic and the results of the selected articles. Finally, a table of results was compiled and the work was completed. **CONCLUSION:** The conclusion of this narrative review is that there is still insufficient scientific evidence in the literature to recommend the widespread use of viscosupplementation in patients with knee osteoarthritis. The main findings of the study were evidence of a mild to moderate analgesic effect, especially in patients with lower Kellgren-Lawrence grades, as well as a slight reduction in stiffness and improvement in functionality. However, no article showed a change in the natural course of the disease, and even in the conflict-free literature, there is great divergence in the results of the studies.
Keywords: Knee osteoarthritis. Viscosupplementation. Intra-articular hyaluronic acid.

INTRODUCTION

OSTEOARTHRITIS

Osteoarthritis is a complex degenerative disease characterized by deterioration of the cartilage that covers the ends of bones. Although it is not often classified as an inflammatory condition, recent research shows that inflammatory processes play a crucial role in its pathogenesis. The release of inflammatory cytokines can accelerate cartilage degradation and intensify joint pain. This interaction between joint degeneration and inflammation makes non-surgical treatment of osteoarthritis particularly challenging, as many conventional therapies may not adequately address this complex dynamic. Thus, the search for innovative therapeutic approaches that consider both degeneration and inflammation is critical to improving outcomes in the management of osteoarthritis (Michael et al[1], 2010; Berenbaum[2], 2012).

This disease predominantly affects the elderly population. In Brazil, approximately 30% to 40% of the elderly have osteoarthritis in some joint, with the knee being the most affected. In this age group, due to a higher probability of surgical complications, there is a growing use of viscosupplementation techniques and conservative approaches, such as

physical activities focused on strength training and weight loss. In addition, the use of non-steroidal anti-inflammatory drugs (NSAIDs), both topically and orally, is an alternative that is considered, although it is important to note that this option has contraindications and may have adverse effects, especially in these elderly patients (Michael et al[1], 2010).

Osteoarthritis is a common joint condition characterized by a series of symptoms that can significantly impact the quality of life of affected individuals. One of the main symptoms is joint pain, which tends to intensify after physical activity or at the end of the day, causing discomfort and limiting the ability to perform daily tasks. This pain can vary in intensity and may be accompanied by periods of relief, but it usually returns after physical exertion (Michael et al[1], 2010).

Another common symptom is joint stiffness, which many patients notice especially when waking up in the morning or after long periods of inactivity. This stiffness can hinder initial mobility, leading to additional discomfort when trying to move. In addition, osteoarthritis can cause swelling in the joints, resulting from inflammation in the affected area. This edema may be visible and palpable, contributing to a feeling of heaviness and discomfort in the affected joints (Berenbaum[2], 2012).

Limited movement is another striking feature of osteoarthritis. As the condition progresses, the ability to move the joint can be severely affected. In addition, many patients report crepitus, a sensation of cracking or grinding in the joints during movement, which can be disconcerting and indicate cartilage deterioration (Berenbaum[2], 2012).

In more advanced cases of osteoarthritis, the joints may undergo visible changes in appearance. Affected joints may appear larger or deformed as a result of cartilage degeneration and abnormal bone growth. It is important to remember that symptoms can vary in intensity and frequency, depending on the severity of the condition and the joints affected (Berenbaum[2], 2012).

VISCOSUPLEMENTATION

Viscosupplementation is a non-surgical treatment used in cases of mild to moderate osteoarthritis. This treatment consists of injecting solutions containing hyaluronic acid directly into the affected joints. Hyaluronic acid is a substance that is physiologically present in joint capsules and acts to lubricate and help cushion impacts. There are also other compounds and materials that can be used for viscosupplementation, such as some types of collagen, dexamethasone, and biological agents derived from trunk cells

However, hyaluronic acid remains the most widely studied and used (Rezende et al[3], 2012).

This treatment is generally used when other conservative options, such as lifestyle changes, physical therapy, topical and oral medications, have been tried and there has been no improvement in symptoms. However, the efficacy of viscosupplementation is not yet well described in the literature. The objective of our study was to conduct a literature review on the topic, proposing a reflection on the benefits of viscosupplementation and clarifying the results of this intervention (Rezende et al[3], 2012).

METHODOLOGY

Like most narrative literature review studies, this work began with a search of available article data sources. This bibliographic search was conducted in the PUBMED database on July 12, 2024, using MESH (*Medical Subject Headings*) with the terms "Knee osteoarthritis therapeutics AND Viscosupplementation." This search resulted in 125 articles that met the search criteria. A filter was added for the most recent publication dates from 2015 onwards, and 56 articles remained after this new filtering. After reading the *abstracts* of

these articles, exclusion criteria were applied regarding conflicts of interest and articles that did not address the use of viscosupplementation as the main subject of the study.

Using these new filters, 17 articles met all the inclusion criteria, including 15 articles in English, 1 article in Spanish, and 1 article in Polish. The articles in English and Spanish were read in their original language by the researchers, while the article in Polish was read with the help of Google Translate. It should be noted that the article in Polish translated into Portuguese was consistent with its *abstract* in English and provided information consistent with the set of articles analyzed.

A total of 17 articles from the 125 found in the search were included in the final work. The 17 articles were read blindly by the four authors between August 2, 2024, and September 2, 2024. After the articles were read by the four independent researchers, a first meeting was held on September 5, 2024, followed by three subsequent meetings between September 5, 2024, and October 2, 2024, during which the topic and results of the selected articles were discussed. Finally, the results table was assembled and the work was checked.

RESULTS

Pereira et al[4](2020) conducted a systematic review study that evaluated the intensity of pain reduction as the primary outcome in comparative studies of hyaluronic acid viscosupplementation versus placebo groups in patients with knee osteoarthritis. As a secondary objective, they evaluated the incidence of adverse effects associated with the use of viscosupplementation. A total of 169 randomized clinical trials were used, involving 21,163 patients with knee osteoarthritis. The analysis of the main objective of the article was based on 24 of these studies, in which a minimal reduction, without clinical significance, in the intensity of arthralgia was observed in patients using intra-articular hyaluronic acid therapy when compared to the placebo group. Furthermore, investigating the secondary objective of the article, an increase in the occurrence of adverse effects was noted in the groups that used viscosupplementation. Fifteen large randomized clinical trial studies, totaling more than 6,400 patients, cite a risk of adverse effects of 1.49% in the control population and 3.7% in the population using hyaluronic acid.

Finally, Pereira et al.[(4)](2020) concluded that there is no literature confirming the benefits of the widespread use of viscosupplementation, as there is no relevant clinical improvement in the field of analgesia. In addition, with the use of hyaluronic acid, there is an increase in potential adverse effects when compared to the placebo groups.

Ferreira et al.[5] (2020) evaluated 40 systematic review studies in a large meta-analysis study and concluded that there is disagreement regarding the effectiveness of viscosupplementation in patients with knee osteoarthritis. This study, however, is still ongoing.

Morales et al[6] (2019) present an observational study that sought to compare high- and low-molecular-weight hyaluronic acid intra-articular therapies in patients with knee osteoarthritis, attempting to ascertain the efficacy and possible improvements in the lives of these patients. To this end, they analyzed 194 patients with Kellgren-Lawrence grade 2 and 3 knee osteoarthritis, in who underwent high and low molecular weight viscosupplementation therapies for comparison. The study evaluated patients using the WOMAC (*Western Ontario and McMaster Universities Osteoarthritis Index)* questionnaire and noted a slight improvement in pain, with no significant differences between high and low molecular weight, with the analgesic effect beginning between 2 and 6 months after the start of therapy and reaching its maximum effect up to 12 months after use.

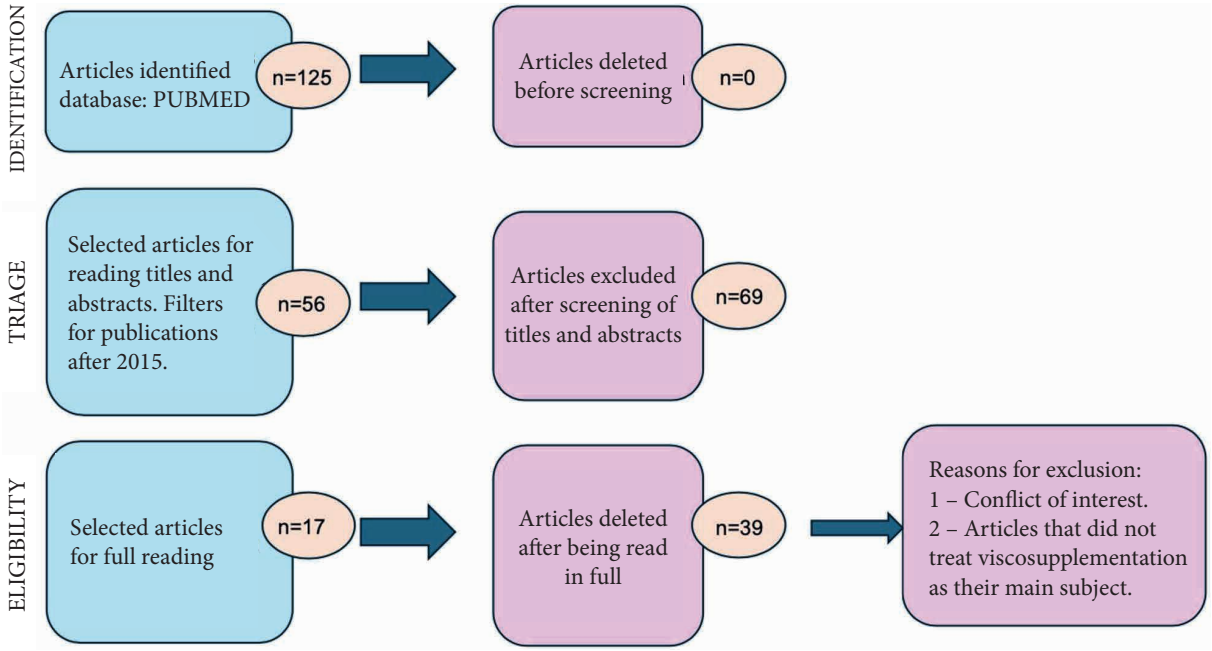

Figure 1 – Literature review flowchart

Source: The authors

Maia et al[7](2019) conducted a randomized clinical trial that sought to evaluate the efficacy of viscosupplementation compared to the use of dexamethasone in terms of pain, functionality, muscle strength, and improved proprioception. To this end, they divided 44 patients with Kellgren-Lawrence grade 1 and 2 knee osteoarthritis into three groups: group 1 with viscosupplementation alone; group 2 with dexamethasone alone; and group 3 with a combination of viscosupplementation and dexamethasone. The patients underwent a WOMAC *score* assessment prior to the intervention and were followed *up* again *6* weeks, 3 months, and 6 months later. They observed an improvement in more intense analgesia in later reassessments with the use of viscosupplementation and viscosupplementation with dexamethasone. In the groups receiving dexamethasone alone, there was an earlier improvement. However, in later assessments, a predominance of better responses to pain, functionality, and increased muscle strength was only noted in the groups using hyaluronic acid. Furthermore, the study states that there was no improvement in proprioception in any of the three groups.

Ludstorm et al[8] (2019) sought to compare viscosupplementation in patients with knee osteoarthritis using ultrasound guidance versus the same therapy guided by anatomical parameters of the knee. Between 2008 and 2014, they evaluated a total of 1,147 patients, of whom 647 received viscosupplementation guided by anatomical parameters and the other 500 patients received ultrasound-guided therapy. The study concluded that there was a better response to intra-articular hyaluronic acid therapy when applied based on ultrasound, with a lower number of patients in the ultrasound-guided group requiring subsequent knee arthroplasty, only 33.2% of patients, compared to 45.8% of those who received the intervention guided by anatomical parameters. The study did not evaluate better response to pain or other parameters observed in other studies, nor did it did not distinguish between low and high molecular weight hyaluronic acid in the rates of subsequent surgery.

Bączkowicz et al[9] (2021), through a clinical trial, sought to evaluate the effectiveness of viscosupplementation in patients with knee

osteoarthritis based on improvements in vibroatrography, with reduced pain, stiffness, and improved functionality using the WOMAC *score*. Furthermore, to continue the study on improved functionality, the ROM (*range of motion)* tool was also used to analyze the joint's range of motion. To this end, they used medium molecular weight hyaluronic acid in 35 patients selected for the study who had Kellgren-Lawrence grade 2 knee osteoarthritis, compared to 50 asymptomatic individuals classified as a control group. In this study, the intervention was guided by anatomical parameters. The researchers concluded that there was a slight decrease in the patients' WOMAC *score*, which was analyzed 1 day before application and 2 and 4 weeks after application, indicating a slight improvement in pain, stiffness, and functionality, since hyaluronic acid infiltration reduces friction in the joint environment, thus restoring its biomechanical properties. With the ROM tool, they noticed greater range of motion after using the therapy and, more revealingly, a significant decrease in the size of the sound waves captured through vibroacoustic emission caused by joint crepitus in the patients' vibroatrography. However, the therapeutic effect is only temporary, since there was an improvement in the parameters collected two weeks after application, but four weeks later, the parameters were already the same as those obtained before injection.

Falkowski et al.[10] (2018) conducted a pilot clinical trial comparing vibroarthrographic parameters in patients with Kellgren-Lawrence grade 2 knee osteoarthritis before and after viscosupplementation. The researchers' findings indicated, through the use of medium molecular weight hyaluronic acid, an improvement in sound parameters noted by lower amplitude waves presented in the vibroarthrography of 17 patients undergoing the study, after the application of viscosupplementation. The researchers attribute this improvement in sound factors to a lubricating effect of hyaluronic acid, which would reduce the level of friction in the affected joint.

Materkowski et al.[11] (2018) analyzed the medical records of 15,000 patients with osteo degenerative knee diseases who used viscosupplementation, seeking to find the efficacy and possible adverse effects of intra-articular use of hyaluronic acid. Through the study of these medical records, they concluded that there is no serious risk to the health of patients who use viscosupplementation therapy.

Xing et al.[12] (2017) conducted a meta-analysis to define the risk of *bias* in other systematic review studies on viscosupplementation in patients with osteoarthritis. To this end, they used the ROBIS *tool* (*risk of bias in systematic reviews*), a tool that assists in responding to the risk of bias in studies. Thus, out of a total of 219 studies found, only 31 of them made the inclusion cut. The findings regarding the risk of bias in the studies were that the controversy over the findings regarding the efficacy and risk of viscose supplementation may be explained by systematic reviews with a high risk of bias. Furthermore, in more than one selected study, the reviews contain discrepancies regarding the placebo used, which may explain the conflicting results when compared to hyaluronic acid.

Campos et al[13] (2017) presented, in a randomized clinical trial, results regarding the efficacy of viscosupplementation compared to other therapies in the management of pain in patients with Kellgren-Lawrence grade 4 knee osteoarthritis. A total of 143 patients were selected and divided into three groups: one group using viscosupplementation alone, another using corticosteroids alone, and a third using a combination therapy of hyaluronic acid and corticosteroids. To analyze the analgesic and functional improvement effects, the researchers applied standardized Lysholm *scores* for pain and KSS (*Knee Society Score)*

scores for pain and functionality. These *scores* were used initially, before the application of the proposed therapy, and 1, 3, and 6 months after the use of the intervention. The results of the study showed similar effects in the three groups. However, as concluded by the authors, although viscosupplementation reduced the patients' pain parameters, the results obtained with triamcinolone (the corticosteroid of choice in the study) were still superior.

Thomas et al[14] (2017) conducted an observational study analyzing the cost and effectiveness of viscosupplementation treatment compared to NSAIDs alone, over a 6-month investigation period. With a total of 401 patients divided into two groups, viscosupplementation and NSAIDs, what they noticed during this study period was a parity in the evolution of results using the WOMAC questionnaire in patients at three points in time: before therapy, 3 and 6 months after, in addition to a minimal difference in monthly expenses between the groups. They concluded that there was no significant difference in cost between NSAID therapy and hyaluronic acid therapy.

Estades-Rubio et al.[15] (2017) sought, through a comparative study, to discover the difference in cost and efficacy between the treatment of knee osteoarthritis with a single dose of stabilized hyaluronic acid viscosupplementation versus 5 applications of regular hyaluronic acid therapy. Fifty-four patients with knee osteoarthritis were divided into two groups, the first group receiving single-dose therapy and the second receiving five doses, with patient progress monitored at 1, 2, 4, 8, 12, and 26 weeks after the first dose. The authors concluded that WOMAC scores decreased more in the groups that received the single-dose therapy, while in terms of costs, an increase in overall expenditure was noted in patients in the second group.

Filardo et al[16] (2016) sought, through a literature review, to present in a single source the possible non-surgical therapies for the treatment of knee osteoarthritis, bringing together their effectiveness and adverse effects. After a thorough analysis of existing therapies, they concluded that there is currently no definitive pharmacological therapy for the treatment of knee osteoarthritis, and that the decision that best fits each individual case should be left to the physician and patient.

Filardo et al.[17] (2015), in a double-blind study, observed the outcome of viscosupplementation therapy versus platelet-rich plasma injections in 192 patients with knee osteoarthritis, divided into two groups. After three weekly injections, the patients were evaluated using the IKDC (*International Knee Documentation Committee)*, KOOS (*Knee Injury and Osteoarthritis Outcome Score)*, EuroQol *visual analog scale*, *and* Tegner *score*.

In addition to these pain scales, ROM (*range of motion*) was also used to analyze functionality. The results of the study demonstrated that the application of platelet-rich plasma was not superior to viscosupplementation.

Pshuck et al[18] (2015) conducted an animal model study to investigate the potential risks and adverse effects of viscosupplementation therapy in knees with osteoarthritis. Twenty--five canine models underwent meniscal release of the knee to simulate osteoarthritis and were divided into five groups: three groups receiving intra-articular hyaluronic acid (with varying doses) and two placebo groups receiving intra-articular saline solution (also with varying doses). These canine patients were examined immediately after the injections and after 6 months, with radiographic, arthroscopic, range of motion, pain, and lameness parameters. The study results indicated improved pain and superior functionality in the hyaluronic acid groups compared to the saline solution groups. In addition, a certain

ARTICLE NAME (YEAR OF PUBLICATION)	AUTHOR	TYPE OF STUDY	ANALGESIA	RIGIDITY	FUNCTION
Viscosupplementation for knee osteoarthritis: systematic review and meta-analysis (2020)	Tiago V. Pereira	Systematic review and meta-analysis of randomized trialsrandomized	Nega	No	No
Viscosupplementation for the treatment of osteoarthritis of the knee: A protocol for an umbrella review of systematic reviews with meta-analyses of randomized controlled trials (2020)	Carlos Augusto Ferreira de Andrade	Review of systematic reviews	No results displayed	No results displayed	No results displayed
Efficacy of viscosupplementation with high and medium molecular weight hyaluronic acid in patients with symptomatic gonarthrosis grades II-III (2019)	E. Vazquez Morales	Observational study	Slight improvement	Not cited	Not cited
Viscosupplementation improves pain, function, and muscle strength, but not proprioception, in patients with knee osteoarthritis: a prospective randomized trial (2019)	Phelippe Augusto Valente Maia	Randomized clinical trial	Improvement	Improvement	Improvement
Rethinking Viscosupplementation: Ultrasound Versus Landmark Guided Injection for Knee Osteoarthritis (2019)	Zachary T. Lund-storm	Comparative study	Does not cite	Does not cite	Does not cite
Effects of Viscosupplementation on Quality of Knee Joint Arthrokinematic Motion Analyzed by Vibroarthrography (2021)	Bączkowicz D.	Clinical trial	Slight improvement	Slight improvement	Improvement
Effects of Viscosupplementation on Knee Joint Arthrokinematics - Pilot Study (2018)	Krzysztof Falkowski	Clinical trial	No citation	Slight improvement	Not cited
Practical Aspects of Hyaluronic Acid Application in Biolevox HA Preparations – Report on Research (2018)	Maciej Materkowski	Case report	Not cited	No citation	No citation
Intra-articular hyaluronic acid injection in treating knee osteoarthritis: assessing risk of bias in systematic reviews with ROBIS tool (2017)	Dan Xing	Systematic review	Not cited	No citation	Does not cite
Viscosupplementation in patients with severe osteoarthritis of the knee: six-month follow-up of a randomized, double-blind clinical trial (2017)	André Luiz Siqueira Campos	Randomized clinical trial	Slight improvement	Slight improvement	Slight improvement
Intra-articular hyaluronic acid in the management of knee osteoarthritis: Pharmaco-economic study from the perspective of the national health insurance system (2017)	Thierry Thomas	Observational study	Improvement	Improvement	Improvement
Knee Viscosupplementation: Cost-Effectiveness Analysis between Stabilized Hyaluronic Acid in a Single Injection versus Five Injections of Standard Hyaluronic Acid (2017)	Francisco J. Estades Rubio	Comparative study	Improvement	Improvement	Improvement

Non-surgical treatments for the management of early osteoarthritis (2016)	Giuseppe Filardo	Literature review	No citation	No citation	No citation
Platelet-Rich Plasma Injections Were Not Better Than Hyaluronic Acid Injections for Knee Joint Degeneration (2016)	G. Filardo	Comment	Slight improvement	Slight improvement	Slight improvement
Hyaluronic acid versus saline intra--articular injections for amelioration of chronic knee osteoarthritis: A canine model (2016)	Troy D. Pashuck	Comparative study	Improvement	Improvement	Improvement
AMSSM scientific statement concerning viscosupplementation injections for knee osteoarthritis: importance for individual patient outcomes (2016)	Thomas H. Trojian	Literature review	Improvement	Improvement	Improvement
Hyaluronic acid in knee osteoarthritis: preliminary results using a four-month administration schedule (2015)	Michele Abate	Observational study	Slight improvement	Slight improvement	Slight improvement

Table 1 – Articles selected by author, type of study, year of publication, and results.

Source: THE AUTHORS

Legend – Table 1:

Improvement: strongly associated Slight improvement: weak association

Not mentioned: the subject is not mentioned in the article Denies: no association

degree of safety was demonstrated in viscosupplementation therapy, with a total of 8 cases of adverse effects noted, 5 in the viscosupplementation groups and 3 in the saline solution groups. This adverse effect of edema and heat in the joint was resolved within a maximum of 1 week after the onset of symptoms, without the need for intervention.

Trojian et al[19] (2015), in a systematic review study, included 11 studies that met the authors' inclusion criteria, comparing patients using viscosupplementation for knee osteoarthritis with placebo groups and groups receiving corticosteroids as a form of intervention. They made the comparison through pre- and post-exposure assessment using the WOMAC questionnaire, which sought to evaluate patients for pain reduction and improved functionality. The authors concluded that, for patients with Kellgren-Lawrence grades 2 and 3 and over 60 years of age, there was a greater improvement in WOMAC *scores* in patients who used viscosupplementation than in those who were part of the corticosteroid or placebo groups.

Abate et al[20] (2015) created a study to evaluate the use of high molecular weight viscosupplementation at 4-month intervals. To this end, they selected 15 patients with grade 2 and 3 Kellgren-Lawrence knee osteoarthritis to receive weekly injections for 3 weeks and, subsequently, a single injection of higher molecular weight that would be applied 4, 8, and 12 months after the start of the study. The analysis of the study was performed using the VAS (*visual analogic scale*) for pain, which was applied at rest and during physical activity. In addition, they used the Lequesne index (a questionnaire that assesses pain and joint function), the KOOS score (*Knee Injury and Osteoarthritis Outcome Score)*, and researched the monthly use of oral NSAIDs for pain relief. This assessment was performed at 1, 4, 6, 8, 12, and 14 months of the study.

Abate et al.[(21)] (2015) concluded, after analyzing the collected data, that patients showed a reduction in the visual analog scale (VAS) of pain at rest and during activity, and that there was a significant decrease in the

monthly oral use of NSAIDs. In addition, the Lequesne and KOOS questionnaires showed an improvement in both *scores*.

The results found after reading and analyzing the selected articles are presented in Table 1 below, which was prepared to facilitate understanding and comparison.

DISCUSSION

For a better understanding of the discussion, the main findings of the studies selected for this paper have been divided into topics, as presented below.

AL ANALGESIC FINDINGS

The analgesic effect produced by viscosupplementation is currently one of the major topics of discussion in both orthopedics and rheumatology. The literature contains a wide range of results regarding the effectiveness of intra-articular hyaluronic acid in combating pain in patients with knee osteoarthritis. Study results vary from very favorable, entering into possible *guidelines,* to the opposite, not recommending its use and highlighting potential risks of application.

The literature selected for this study mostly analyzes viscosupplementation in its role as a pain-reducing therapy in patients with knee osteoarthritis. This analgesic effect was evaluated in 11 of the studies, with a predominance of mixed findings, little indication, or slight improvement. Of these 11 articles, 6 used the WOMAC questionnaire, a 24-item questionnaire that analyzes 3 subscales: pain, stiffness, and functionality, to analyze patients after the use of viscosupplementation. Four studies used a control or comparative population, with a wide range of therapies for comparison, such as the use of intra-articular corticosteroids, intra-articular saline solution, or platelet-rich plasma injection. As mentioned above, what was observed was a predominance of inconclusive findings of significant pain improvement, the most common being a slight but significant analgesic effect, mostly in patients with milder degrees of knee osteoarthritis (Kellgren-Lawrence grades 2 and 3), these Kellgren-Lawrence grades being the most analyzed in the selected studies. It should be noted that the vast majority of the selected studies excluded patients with surgical indications and/or with previous use (varying in length, but not exceeding 2 years) of viscosupplementation and/or intra-articular corticosteroids and/or intra-articular NSAIDs, and patients with osteoarthritis of rheumatological causes and/or systemic diseases.

It is possible to observe in most studies, both those with favorable results and those with unfavorable results, the lack of suspension of other non-pharmacological therapies during the study period. Some studies clearly provide guidance on weight loss and physical exercise for study participants, which are pillars of non-pharmacological treatment for knee osteoarthritis and could partly explain the improvement in patients' pain symptoms. Another therapy that appears in conjunction with the use of the analyzed therapy is the use of oral NSAIDs, which has even been explored in some of the studies. Inversely related to its use and the duration of viscosupplementation therapy, there is a decrease in the use of oral NSAIDs during times of severe pain, with improvement in symptoms provided by the test therapies in both the viscosupplementation and comparative groups. In short, there is a decrease in the need for other pharmacological therapies for pain relief. Regarding the non-pharmacological therapies that were used concomitantly, they cannot be dissociated from the results of pain improvement; however, it is also not possible to credit all clinical improvement in isolation to adjunctive therapies.

Regarding the use of low or high molecular weight hyaluronic acid and its respective analgesic performance, a predominance of more satisfactory effects in pain reduction therapy was found with the use of high molecular wei-

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ght hyaluronic acid. More than one study has proposed this comparison, with a more favorable outcome, albeit with a small difference, with higher molecular weights, and there are two theories to explain this. One would indicate proximity to physiological molecular weight (which tends to be higher), hence the better results, while the other proposes an inverse relationship between pain and molecular weight (the higher the weight of hyaluronic acid, the less pain). This preference pattern was noted in all studies that proposed this comparison in relation to pain, which was not seen in its entirety when comparing other effects of viscosupplementation, which are discussed later in this paper.

Regarding the follow-up time and number of applications required, the articles differ in certain aspects. Even with some divergence in results, it is possible to associate a longer time for the onset of analgesic effects with intra-articular therapy with hyaluronic acid than with other intra-articular therapies using corticosteroids, which had earlier effects in reducing pain symptoms. However, corticosteroids, compared to viscosupplementation, also have an earlier end to their effect, usually when the effects of viscosupplementation begin to appear (around the twelfth week after the use of therapies). The combined use of viscosupplementation and intra-articular corticosteroids has also been the subject of some studies, with mixed results, and no therapy has been found to have both early and long-lasting effects.

The disagreement seen in the results regarding analgesia with the use of viscosupplementation in some of the selected articles could also be explained by the low number of participants, the short follow-up time, methodological flaws, and the lack of a control group in some of the articles. However, given the conflict-free evidence, the potential pain--reducing action of intra-articular hyaluronic acid cannot be denied.

Finally, the findings regarding the analgesic effect of viscosupplementation can be summarized as clinically relevant, with no studies contradicting the improvement in pain in patients using this therapy. However, it should be noted that, in some studies, this effect is comparable to that of other established therapies, and in others, it is still comparable to the placebo effect. Nevertheless, in some studies on the analgesic effect of viscosupplementation, there is no control group, making it impossible to obtain an overview of the improvement in the natural course of the disease. Another factor contributing to the low credibility of findings that strongly indicate viscosupplementation for pain would be the difficulty of separating the isolated contribution of intra-articular therapy from that of weight loss and physical exercise recommended in the care of patients with knee osteoarthritis, without excluding, however, the participation of viscosupplementation in pain improvement. Furthermore, there is a certain agreement between articles on the best effects of using high molecular weight hyaluronic acid and articles that show an improvement more marked in *scores* of pain bring a follow--up with multiple applications of intra-articular therapy.

FINDINGS REGARDING THE REDUCTION OF RIGIDITY

Continuing research into the effectiveness of viscosupplementation, the most recent studies on this therapy attempt to evaluate not only its analgesic effects, but also its ability to improve functionality. The reduction of joint stiffness, known as ankylosis in technical terminology, would then be one of the main factors related to this functional improvement in the affected knee. This is one of the predominant complaints of patients with knee osteoarthritis and a subject of study for many researchers.

In order to compare the behavior of intra-articular hyaluronic acid in improving joint stiffness with other available therapies and with placebo groups, the selected intervention study articles used assessment *scores*, using KSS (*Knee Society Score*) and WOMAC (*Western Ontario and McMaster Universities Osteoarthritis Index*). These *scores* assess the patient's perception of improvement in stiffness and were applied in most studies prior to the analysis therapy and during follow-up, with some studies attempting to assess short--term efficacy with reevaluations in the weeks following intervention, while others considered the long-term action of viscosupplementation, reevaluating the patient in months of study, in the same way as the evaluation of the analgesic effect. Since most of these *scores* do not evaluate only stiffness, it makes sense to apply them in conjunction with the evaluation of other effects of intra-articular hyaluronic acid therapy.

Given this, it can be concluded that viscosupplementation has an effect against stiffness, which is typical of patients with knee osteoarthritis, with improvements in *the scores* used in pre- and post-exposure assessments of the proposed intervention, superior in some cases to those of other techniques used for comparison. However, it should be noted that there have been no publications reporting improvement in stiffness in patients with more advanced degrees of osteoarthritis, with improvement noted improvement only in patients with Kellgren-Lawrence grades 2 and 3, which are also the groups most commonly used for these studies. Furthermore, of the studies that mention improvement in stiffness, the vast majority do not have a comparative population, making it impossible to compare with another therapy or placebo.

FINDINGS REGARDING IMPROVEMENT IN VIBROARTHROGRAPHY ( )

Vibroarthrography (VAG) is a non-invasive technique that analyzes the sound waves generated when listening to the crepitus formed during movement of the joint being studied. In this exam, graphs are generated based on the frequencies of the waves for analysis and comparison of joint sound. This technique was used in three of the selected articles to identify possible improvements in crepitus sound with the use of viscosupplementation.

The findings of this examination in patients with osteo degenerative diseases, as well as in patients with knee osteoarthritis, are waves with higher sound peaks, composing graphs of greater amplitude, which corresponds to the sound of increased joint crepitus due to the degeneration of the synovium and its associated elements, generating a sound resulting from friction caused by the loss of part of the protective cartilage of the joint. In the selected studies that addressed this change with viscosupplementation therapy, what was observed was a decrease in the amplitude of sound waves in vibroarthrography compared to the same exam performed prior to the injections. The sound levels, however, did not reach the amplitude of asymptomatic patients, used as a control group.

The authors attribute the improvement in sound patterns observed in vibroarthrography to the possible lubricating effect of viscosupplementation, which would bring greater fluidity to the synovial environment, resulting in decreased friction and contact, which would cause a decrease in the observed changes in sound amplitude. One observation regarding the molecular weight used would be the lack of evidence on differences between high and low molecular weight, as only medium molecular weight hyaluronic acid was used in the articles that employed this technique.

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Thus, there is a lack of literature discussing possible differences in VAG results when using different molecular weights of hyaluronic acid. Furthermore, it should be noted that few studies have addressed viscosupplementation from the perspective of vibroarthrography, which was mentioned in only 3 of the 17 studies used to prepare this paper.

In summary, there was an improvement in crepitation patterns in patients using viscosupplementation, which was noted by lower sound wave amplitude patterns in vibroarthrography, with a decrease in waves prior to exposure to the intervention technique compared to waves in post-exposure exams, which may indicate a decrease in bone friction typical of osteo degenerative diseases. However, in addition to the few studies that address the topic from the perspective of vibroarthrography, and of these few studies, none involving a large number of patients, the improvement in VAG is still accompanied by little clinical improvement in terms of pain and stiffness reduction.

FINDINGS ON FUNCTIONAL IMPROVEMENT

Although decreased joint stiffness may be associated with improved functionality, there are other factors that contribute to this improvement. In the selected articles, improved functionality was analyzed, as were improvements in pain and stiffness, using *scores*, the main one being WOMAC, which, as mentioned above, can be divided into topics related to pain, stiffness, and functionality. In addition to the WOMAC *score*, the ROM (*range of motion)* score was also used, which assesses the range of motion of the joint and is one of the main measures used to assess functionality in knee osteoarthritis, as well as the KOOS *score*, which assesses pain, joint stiffness, and functionality.

The data collected in the selected studies indicate a slight improvement in *scores* related to functionality and other parameters, such as the aforementioned KOOS and WOMAC *scores*. However, in some of the articles that present results from these analytical tools, there is no indication of which *score* parameters improved, making it impossible to make a concrete statement about improved functionality. From those that present the results of *the* distinguished *scores*, there is an improvement in the functionality parameters, especially in Kellgren-Lawrence grade 2 and 3 patients. Regarding ROM (*range of motion*), in the studies that used this measure, there was an improvement in the range of motion of extension and flexion of the affected joint after the use of viscosupplementation.

In summary, the studies presented two main ways of assessing functionality: *scores* for evaluating various parameters (KOOS and WOMAC) and the measurement of range of motion (ROM). In the use of *scores,* there was some divergence among studies, with some showing improvements in absolute values but not stating which factors contributed to this improvement. In other articles, however, the parameters were discriminated, and there was an improvement in the functionality subtopics of *the scores* after the use of intra-articular hyaluronic acid. Furthermore, for the few studies that used joint range of motion measurement, there were improvements in extension and flexion values, indicating functional improvement.

FINDINGS REGARDING ADVERSE EFFECTS AND S S

The study of adverse effects of therapies that are not yet consolidated is of paramount importance because it provides information that can guide decisions regarding interventional medical conduct. Therefore, thorough research is needed on the possible risks of in-

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tra-articular hyaluronic acid application. Of the studies included in this work, five cite the occurrence of adverse effects, which were observed in greater numbers in the population using viscosupplementation than in the control groups. One of the largest meta-analysis studies ever conducted on the subject noted that in a group of studies involving a total of 6,462 patients with knee osteoarthritis, there was an incidence of adverse effects of 3.7% in patients using viscosupplementation, a much higher number when compared to the 1.49% risk of adverse effects found in the control groups.

In short, there is a pattern suggestive of risks associated with intra-articular hyaluronic acid therapy. Therefore, further studies are still needed to reveal the adverse effects associated with viscosupplementation, further investigation into the risks of hyaluronic acid application, and the long-term effects after using this therapy.

FINDINGS REGARDING THE BEST FORM OF ADMINISTRATION OF

A topic that has been little explored in recent studies, but is no less relevant, is the best form of viscose supplementation application. Referred to in few of the selected studies, there is currently a question regarding the ideal form of intra-articular hyaluronic acid application, with the main lines of thought being application guided by anatomical parameters (the most used in the selected studies) or guided by ultrasound, which theoretically would bring benefits because it is more accurate.

The literature selected for this study contained few findings of significant relevance, with a lack of data regarding improvements in efficacy in one form of application or another. The biggest and most important difference between the two forms of application was a higher incidence of knee arthroplasty in patients who had previously used viscosupplementation guided by anatomical parameters, when compared to patients who had used it but guided by ultrasound. In short, there is no concrete evidence of better analgesic effects, improvement in stiffness, or functionality when comparing the ultrasound-guided and anatomical parameter-guided groups. Furthermore, there is a tendency to choose ultrasound-guided application given the lower number of surgical outcomes; however, there is no evidence of the use of viscosupplementation as a curative therapy in patients with knee osteoarthritis. Therefore, these data, although important for analysis, require further study, as they do not correspond to a conclusive scenario.

CONCLUSION

The literature available today does not contain sufficient scientific evidence to recommend the widespread use of viscosupplementation. The selected studies suggest an analgesic effect of little clinical significance when compared to other intra-articular therapies or the placebo effect. Regarding the improvement of stiffness and functionality, intra-articular hyaluronic acid therapy presents results similar to those of analgesia, with little impact. The great improvement presented comes in the parameters of vibroarthrography; however, with no clinical improvement, this result of the reduction in the amplitude of sound waves caused by the crepitations of kinetic friction of the knee joint is of little relevance. In addition, adverse effects were found which, even with low incidence and minor importance, should be taken into account when calculating the risk versus benefit for the patient.

Finally, there is no evidence in current studies of a slowdown in the natural course of the disease, so it cannot be used as a curative therapy and is only indicated for the relief of associated symptoms. Given this scenario, there is a need for further studies on the use of viscosupplementation in patients with knee osteoarthritis, with the aim of better defining this therapy, its indications, and benefits.

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