Does the use of hyaluronic acid viscosupplementation prolong the viability of a patient's knee with osteoarthritis, delaying the need for surgical management? A systematic review of the literature

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Abstract

Introduction: Osteoarthritis of the knee is a very common complaint in the aging population and a significant burden on not only the patient, causing pain, decreased mobility and a lowered quality of life, but also the healthcare system with frequent primary care visit associated with its symptoms. We investigated the use of viscosupplementation with hyaluronic acid and how long improvement was sustained, preventing the need for costly total knee arthroplasty.

Methods: Using Medline (OVID) search strategy from 1946 until February 2016 was developed with they guidance of library personnel trained in research. We searched for studies that looked specifically at the amount of time that a patient would be able to continue using their knee with appropriate level of function and pain before the gold-standard of treatment via total knee arthroplasty would need to be performed. Titles and abstracts of articles were read to determine if appropriate and four articles met the inclusion criteria which meant the articles must look specifically at how long the use of viscosupplementation prevented the need for total knee arthroplasty.

Results: In all four articles the time to total knee arthroplasty was increase over no treatment. In all the studies they calculated average time to total knee arthroplasty based on the point in which half the knees treated by viscosupplementation required surgical intervention. The range in these studies saw a prolongation between 370 to 919 days over the control groups which were patients whom did not receive viscosupplementation. It was also found that in patients who were considered positive responders, the more courses of viscosupplementation received, the longer the delay of surgical intervention.

Conclusion: Based on the research reviewed it can be said that the use of viscosupplementation vs. no treatment or failed conservative treatment delays the need for total knee arthroplasty in patient with knee osteoarthritis. Further research must be done with more high quality studies using controls to

improve the accuracy of this information. Also, further research should be done to determine if these positive results would in turn lead to savings for the Canadian healthcare system and how best to implement them.

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Introduction

Pathophysiology of Osteoarthritis

Osteoarthritis (OA) is characterized by a degenerative process with loss of articular cartilage, osteophyte formation, subchondral bone remodelling and chronic inflammation of the synovial membrane in its clinical state. (1) The onset of OA, although not completely understood, appears to be associated with factors including: mechanical, biological, biochemical, molecular, and enzymatic feedback loops. In its final state, cartilage destruction occurs due to failure of chondrocytes to maintain balance between matrix synthesis and destruction. (1) As the progression of OA occurs, the catabolic process eventually exceeds the anabolic one, causing loss of cartilage with eventual eburnation of bone. Typically, during the clinical stage of OA there will also be an inflammatory reaction of the synovial membrane causing an increase in the presence of inflammatory mediators which alter chondrocyte metabolism, thus increasing catabolism and decreasing anabolism. (1)

Knee OA in the Canadian Population

OA is the most common form of arthritis and in 2011 it affected 4.4 million Canadians nation-wide with this number being expected to increase to over 10 million within the next 30 years. (2) It plays a large role in long-term disability among the Canadian labour force and it is anticipated in this time that up to 30% of the employable workforce will have difficulty working due to OA. (2) It is also estimated that up to 500,000 Canadians will be suffering with moderate to severe disability from the disease. (2) The major consequence associated with OA is pain leading to both activity and workplace limitations. It is typically more prevalent in woman (18%) than men (9.6%) in the population over the age of 60. (3) It is generally considered a disease of age with many primary care visits being associated with its signs and symptoms.

The two greatest risk factors for OA are ageing and obesity. The Canadian population on a whole is living longer than ever before, and the baby boomers are reaching the age where OA becomes most prevalent. Along with this, obesity rates have been on the rise over the past 40 years with a rate of 9.7% in 1970, now sitting at an astounding 25.3% as a nationwide average. (4) Given these statistics it is apparent that the burden of OA is only going to increase, and cost-effective management strategies are of the utmost importance to minimize disease burden, both from a patient quality of life as well as a healthcare expenditure standpoint.

Current Treatment Methods for OA of the Knee

There are generally two approaches to the treatment of knee OA, the first step being conservative management which involve a number of different modalities including: exercise/physical therapy, bracing/orthoses, nonsteroidal anti-inflammatory drugs (NSAIDs), and intra-articular injections including, viscosupplementation with hyaluronic acid (HA) along with corticosteroid injections. (5) These modalities work through various methods and can often be used in combination to have synergistic effects. The second method of knee OA treatment is surgical and typically is not performed until conservative methods have been exhausted. The surgical methods used for treatment of knee OA include: arthroscopy, high tibial osteotomy, uni-condylar knee arthroplasty, and total knee arthroplasty which is generally considered the final treatment option for knee OA. (3)

When looking at the evidence regarding use of these modalities there has been numerous studies with variable results, some having strong evidence for their application while others are not currently being recommended. Currently, both land and water-based exercise, along with physical therapy are recommended as appropriate intervention for treatment of knee OA. (6) Evidence of effectiveness is apparent. There is no specific emphasis on a particular exercise, but rather a combination of both strength training and aerobic exercise. (6) The evidence regarding bracing and orthosis currently is

considered favorable when recommendations are made by an appropriate specialist, these recommendations being based on fair quality of evidence. (6) Regarding the use of NSAIDs, it is currently recommended as appropriate for those who are at low risk for gastrointestinal bleeds, cardiovascular disease and renal impairment. If any of the prior- listed issues are present, appropriate co-therapy is required. (6) Intra-articular corticosteroids have recently been demonstrated to provide clinically significant short-term decreases in pain. They are recommended as an appropriate treatment option based on good quality evidence. (6)

Current Viscosupplementation Research

Regarding viscosupplementation with hyaluronic acid, the evidence has been quite variable with different recommendations being made for and against its use. A meta-analysis done in 2011 suggested that intra-articular HA used for the treatment of OA pain had a modest effect that exceeded a minimally clinically significant threshold. (7) The most recent recommendations of the American Academy of Orthopedic Surgeons (AAOS) in 2014 strongly recommends against the use of viscosupplementation for treatment of knee OA, reporting that previously-conducted meta-analysis and research presented a publication bias, with publicizing of only the generally favorable studies. (8)

One year after the AAOS recommendation, the American Medical Society for Sports Medicine (AMSSM) revisited the AAOS research related to the use of HA, determining that the methodology used for examining whether the effects of intra-articular hyaluronic acid injections were clinically significant had been flawed. (9) The AAOS study used a new outcome measure, the minimum clinical important improvement (MCII). (9) This guideline has not been approved for individual use in guiding clinical decision making and does not seem to account for variability in age, treatment type, baseline symptom level or trial assessment intervals. Based on this information, when the AAOS used the MCII to develop cut-off values for treatment efficacy, they may have been higher than the appropriate level biasing the

results leading to fewer studies being considered clinically relevant. (8) Eleven articles met the AMSSM inclusion criteria. Each article included intra-articular HA, intra-articular steroid (IAS), and intra-articular placebo (IAP) as the different methods of treatment and control. They found that the intra-articular HA injection group showed a small but statistically significant improvement compared to the IAS and IAP in regards to pain and function based on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). (19) Also, the study showed an 11% greater chance of meeting the Outcome Measures in Rheumatoid Arthritis Clinical Trials – Osteoarthritis Research Society International (OMERACT-OARSI) responder status than IAP, and 15% greater chance than IAS, which are both statistically significant. Based on these most current results, the AMSSM recommends viscosupplementation injections for knee OA falling in the Kellgner-Lawrence grade II-III for those aged of 60 or over, based on high quality evidence, and suggest the use of viscosupplementation injections for knee OA on those under the age of 60 years based on moderate quality evidence due to the response of treatment in those over 60 years of age. (9)

Another study done in 2014 by the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) (10) which performed a meta-analysis of the literature recommends the use of hyaluronic acid, suggesting that a course may have longer-lasting effects, up to six months, which is longer than most pharmacologic measures. There is no significant difference in efficacy when compared to oral NSAIDs which are considered one of the most effective non-surgical methods of OA treatment. They also go as far as saying that in patients who have contraindications to NSAID use, HA injections may be a good alternative. (10)

Based on the research gathered by the AMSSM and ESCEO, it is reasonable to say that viscosupplementation is an appropriate conservative method for the treatment of knee OA. (9,10)

The Theory Behind Viscosupplementation

The majority of treatments for knee osteoarthritis aim at altering the pain associated with degradation of the various components of the knee such as NSAID and corticosteroid use, as well as slowing progression of the disease process by reducing stresses on the knee through exercise and weight reduction. The theory behind hyaluronic acid is different than these methods as it looks to emulate the viscoelastic properties of synovial fluid within the knee, which is altered with osteoarthritis. As the disease progresses, there is increased collagen turnover, decreased proteoglycans, as well as decreased hyaluronic acid molecule size and concentration. (11)

The HA itself is responsible for viscoelastic properties of synovial fluid acting as both a shock absorber and lubricant. It is expected that because the HA coats the articular cartilage and shares space deeper within the cartilage, it may play a role in cartilage protection by helping to maintain the cartilage matrix. It may also help to prevent migration of inflammatory cells into the joint space. (12) Viscosupplementation is thought to also help facilitate the synovium to produce more HA. In research, high molecular weight viscosupplementation agents were shown to produce a greater synthesis of HA than lower weight preparations. (13) Regarding the relief of pain associated with knee OA, the benefit of HA is likely due to its effects on nerve impulses and sensitivity as well as being associated with prevention of inflammatory mediators from entering the synovial fluid. With inflammation in the knee joint, this increases the excitability of nociceptors and articular nerves. In OA the nerves become allodynic and fire spontaneously, becoming sensitive to non-noxious movements. The injection of HA has been shown to decrease the ongoing sedentary nerve activity, along with nerve activity caused by movement up to 60% compared to controls. (14)

Viscosupplementation is considered to be a safe treatment option for knee OA but there are still small potential risks involved with the injection. The most common side effects are pain and swelling at the

injection site, (15) and there has been reports of pseudoseptic reactions. (10) The contraindications to the use of HA injections include hypersensitivity to HA, presence of a local joint infection, or the presence of a local skin disease or infection of the overlying skin in the knee requiring injection. (15)

There has been significant prior research looking at whether it was effective at alleviating the symptoms associated with knee OA (8–10) but there had been very little research looking at the actual amount of time that viscosupplementation prevents the need for replacement. Having information like this available would open the door to further research in regards to whether viscosupplementation is cost-effective for the system, and can look at which sub-groups of patients the application would be most practical and beneficial on. An example of this would be knowing that TKA only last for a certain period of time before revision is required, could viscosupplementation be used to bridge the gap between traditional conservative methods and TKA at the point where revision surgery is less likely to be required?

The purpose of this systematic review is to look at whether viscosupplementation with hyaluronic acid is effective at delaying the need for surgery in patients with OA of one or both knees. The patient population must not have any other contributing comorbid factors (meniscal injury, ligamentous injury, etc.) and must have exhausted other conservative treatment methods (NSAID's, physical therapy, etc.). An improvement in pain and function of the viscosupplementation group vs. no treatment vs. placebo would be considered a positive response, and more specifically, the actual length of time this decrease in pain and increase in function delays need for TKA.

Methods

Search Strategy

A Medline (OVID) search strategy was devised with guidance from a librarian trained in research to identify articles which specifically looked at the amount of time a patient's knee with osteoarthritis could be effectively used after a treatment course of intra-articular viscosupplementation with

hyaluronic acid, before total knee arthroplasty would become the recommended treatment strategy. The Medline (OVID) search engine gathered information from 1946 until February 2016. Search terms included:" viscosupplementation" OR "hyaluronic acid", "knee osteoarthritis", "total knee arthroplasty". These search terms were then combined to include term "1" AND "2" AND "3", resulting in twenty articles to be reviewed. The abstract from each of the articles was read and full articles accessed, if required, to identify those of relevance.

Study Selection

The majority of these articles did not look specifically at time to total knee arthroplasty, but rather at whether viscosupplementation was effective in OA treatment. No language limits were applied. Of the twenty articles reviewed, four looked specifically at how long patients were able to prevent the need for total knee arthroplasty using viscosupplementation and were included in our study. (15–18) Due to the very limited number of articles that looked specifically at the data we were wishing to review, all studies that were identified were included, with the only inclusion criteria being the use of viscosupplementation with HA and time until total knee arthroplasty was required.

Results

Study Characteristics and Populations

Of the four articles included, there was one retrospective records evaluation, one prospective cohort study, one retrospective case series and one retrospective cohort study. With this variability in the type of study performed, there were obvious differences in the methodology each party used to collect and analyze information, although there were some common patterns of information collected in each study. The selection criteria of patients did include some variability, but the majority of pertinent patient

data which was the same included: age, gender, Kellgren-Lawrence classification and 0-100 mm visual analog scale (VAS) (19) with Altman Et. El. and Waddell Et. El. (15,17), absence of other mechanical knee problems (severe varus/valgus deformity, end-stage bone on bone disease, ligamentous damage, etc.) along with failure of other prior conservative treatment. Research done by Turajane Et. El. (18) used the Ahlback radiological rating system of OA which looks at the presence of joint space narrowing with a grading scale of 1 through 5, with one being minor narrowing of the joint space and 5 being major attrition of the bone with possible subluxation. (20) All studies also excluded any patients in which intra-articular HA injections were contraindicated, such as HA sensitivity or allergy, underlying joint infections, or overlying skin infections of affected joint.

Several different methods were used to determine whether the use of HA injections continued to be adequate treatment for various stages and measurements of knee OA. The retrospective records evaluation done by Altman et. El. (15) did not look directly at methods of determining need for surgical intervention as they were accessing data from a database of ~79 million patients and did not go into detail regarding methods used to determine replacement need. It did, however, look at the number of courses of HA injection each patient was given, along with the change in time until TKA. The database used was the IMS Health PharMetrics Plus database which includes all Metropolitan Statistical areas in the United States. Turajane Et. El. (16) used the Western Ontario and McMaster Universities Arthritis Index (WOMAC) which required a decrease of 20% from the patient's baseline score to prevent surgical interventions, while Waddell Et. El. (15) required a decrease of greater than or equal to 20 mm on the 0-100 mm VAS after administration of HA. Romero Et. El. (16) referred patients for TKA based on two conditions: 1) Patients with Kellgren-Lawrence grade 4 disease minus those who had contraindications to surgery or over the age of 75. 2) Patients with Kellgren-Lawrence grade 3 disease that was disabling or refractory to standard pharmacological treatment including analgesics, NSAIDs, corticosteroid injections or disease-modifying drugs such as HA, as long as the patient was 60 years of age or older.

In regards to pertinent patient data, the age of patients was variable, the youngest identified patient was 28 years of age although one study only reported patient numbers via a range from 18-44 years, and the most elderly patient involved being 98 years of age. The majority of patients within the study were between the ages of 50 and 80 years. In the research done by Romero Et. Al. (16) there was suggestion that the use of viscosupplementation in patients 65 years of age and older was more beneficial than patients under the age of 65 with a median time to TKA of 1278 days versus 945 days. This was similar to the reported data by Trojian Et. El. (9) mentioned previously. The predominant gender in all four studies were female ranging between 61.5% and 74.9% which falls in line with research regarding sex prevalence of knee OA. (21)

Again, based on the variability of these different types of studies, the sample size and control groups were quite variable. The largest sample size was 182,022 patients who met the inclusion criteria for the study done by Altman Et. El. (17), 224 patients with Romero Et. El. (16), 183 patients with Turajane Et. El. (18) and 863 patients (1187 knees) in the study by Waddell Et. El. (15). One other important relevant piece of information to note is that each study used a different formulation of viscosupplementation including hylan G-F 20 (Synvisc), 500-730 kilodalton sodium hyaluronate (Hyalgan) and stabilized hyaluronic acid (Durolane) which is the only single injection formulation, with others requiring three administrations to be considered one course of treatment.

When looking at the data collected the studies reported both mean and median numbers. All of the studies used the time in which 50% of patients received TKA as their reference point when comparing control versus the intervention group and determining the number of days/years until TKA was required. Control groups were not very well defined with two of the studies not having any form of control group, one study having only 22 patients as a control and the meta-analysis having a large number of 131,673. With Waddell Et. El. research they admit that this is a limitation to their study but in the same light say that with their normal surgical population not receiving HA injections, typically they

will have TKA done within three months, and a large portion of patients felt treatment with hylan G-F 20 was effective enough to warrant multiple courses of injections (44.9%).

Individual Study Primary Outcomes

The actual numbers presented in the studies all showed, on the whole, an increase in the amount of time until knee replacement with the use of intra-articular HA. In the study done by Altman Et. El. (17) half of all patients diagnosed with knee OA that did not receive HA injection had a TKA by 114 days. In the same study, it took 484 days for half of patients with HA injection to progress to TKA. A Cox proportional hazard model was used in order to determine the "risk" of having a TKA based upon the number of HA courses a patient received, when the patient's age, gender, and comorbidities are included as background covariates. Although the hazard ratios also considered age and gender as statistically significant, they did not influence "risk" of TKA as much as HA injection did. Of the patients receiving HA treatment, 73.2% received one course, 17.7% two courses, 5.5% three courses, 2.1% four courses and 1.5% greater than or equal to five courses. In non-HA patients the mean time to TKA was 255 days (0.7 years), with one course of HA 510 days (1.4 years) and with five or more courses 1314 days (3.6 years) with ~22% of patients receiving five or more courses delaying TKA by 1643 days (4.5 years) or more. (17)

In the study done by Waddell Et. El. (15) as mentioned previously there was no control group but typically those presenting as surgical knee OA candidates would receive a TKA by ~3 months in their particular practice. All patients received at least one course of hylan G-F 20. During the follow-up period, 225 knees (19%) underwent TKA. In this study they looked at median time until TKA during the follow-up period which was 638 days (1.8 years). For knees that did not undergo TKA during the follow-up period, the median follow-up time was 810 days (2.2 years). Survival analysis was also performed to

analyze all knees for time to TKA, which suggested that 75% of patients would not have had a TKA done by 1370 days (3.8 years with a 95% confidence interval (CI)).

The 54-month follow-up study done by Turajane Et. El. (18) was also uncontrolled, but each patient was required to have at least six months of non-invasive treatment without effective result which allowed them to be a candidate for TKA. The patients were divided into three groups based on their Ahlback radiographic findings with group 1 being Ahlback grade 1 and 2, group 2 Ahlback grade 3 and 4, and group 3 being Ahlback grade 5. Increasing grade is equal to more advanced OA. In the 54-month follow-up the occurrence of TKA was 28.4% with a mean time to TKA of 468 days (1.3 years). In group 1 19.6% of patients received TKA, while group 2 had the highest rate of TKA at 35.7% and group 3 at 26.9% respectively. 71.6% of patients were considered positive responders to treatment and had a mean follow-up time of 1387 days (3.8 years). In respects to groups 1, 2 and 3 that underwent TKA, the average number of HA courses received were 1.44, 1.2 and 2.5 respectively. In those who did not undergo TKA within groups 1, 2 and 3 the average number of courses was 5.46, 6.11 and 6.08. The average delay in time to surgery per course of HA was calculated to be 234 days (0.64 years). With the use of survival analysis, it was predicted that 75% of patients would not require a TKA by 1177 days (3.23 years). (18)

In the study done by Romero Et. El. (16) there was a control group of 22 patients versus the HA group of 202. With regards to Kellgren-Lawrence classification, 9% were grade 1, 25.5% were grade 2, 48.2% were grade 3 and 15.3% were grade 4. Again, an increase in grade indicated more advanced OA. Of the 22 patients in the control group, 2 (9.1%) were referred for surgery and 38 (11.9%) in the HA group were referred. With the sample size being so small for the control group it is difficult to consider this a significant finding. The mean time to surgery in patients not receiving viscosupplementation was 694 days (1.9 years) while those receiving viscosupplementation was 1093 days (3 years). In this study they used Cox regression to assess other variables that affect time to surgery. Those that were statistically

significant with a 95% confidence interval included the number of affected joints, with having one joint affected decreasing the time until surgery, the severity of arthritis with higher severity causing shorter time until surgery, and pain intensity on the VAS with higher intensity resulting in a longer time until surgery.

Table 1. Comparison of Pertinent Study Information and Results

	Altman Et. Al.	Romero Et. Al.	Turajane Et. Al.	Waddell Et. Al.
Type of Study	Retrospective Evaluation of Records	Retrospective Cohort Study	Prospective Cohort Study	Retrospective Case Series
Total Sample Size	182 022 patients	224 patients	183 patients	1187 knees (863 patients)
Control Group Size	131 673 patients	22 patients (HA vs no HA)	No control	No control
Gender	No. %	No. %	No. %	No. %
Male	77 014 42.3	72 32.1	46 25.1	481 40.5
Female	105 008 57.7	152 67.9	137 74.9	706 59.5
Mean Age	61.0 years	65.7 years	68.7 years	67.4 years
HA Formulary Used	Unspecified	Stabilized Hyaluronic Acid (Durolane)	500-730 Kilodalton sodium Hyaluronate (Hyalgan)	Hylan G-F 20 (Synvisc)
Time Until Half of patients had TKA with HA	484 days (up to 1643 days in HA responders)	1093 days	"Responders" with multiple HA injections 1387 days	772 days (to the time of TKA or lost to follow-up)
Time Until Half of Control had TKA	114 days	694 days	HA "non-responders" 468 days	No active control – statistics from their practise show TKA normally done within 3 months

Discussion

The goal of this paper was to determine if the use of HA injections increased the time before TKA was required compared to patient not receiving HA, and if so specifically how long that time increase is. The research papers reviewed showed a decrease in pain and improved function quantified with various assessment tools when HA injections were used on patients with OA of the knee. This in turn lead to improved quality of life for the patients resulting in an increase of time until TKA was performed.

Importance of Findings

This information is important to know for a number of reasons. First of all, the majority of pharmacological treatments only provide very short term benefits in terms of pain reduction and functional improvement. Medications such as NSAIDs must be taken daily, and even treatment such as intra-articular corticosteroids in most cases only provide a statistically significant difference in pain up to 1-week post-injection. (22) The use of viscosupplementation, although it can take a number of weeks to have an effect, has shown to have beneficial changes in pain and function months after injection (7) which is important because of the decreased need for medication administration. Some of the research also pointed out that in patients whom responded positively to the first administration of HA also had a positive effect with subsequent treatment, again further preventing need for TKA. (15,17,18) The large study done by Altman Et. Al. showed that the mean time to TKA in patients receiving greater than or equal to 5 HA injections was 1306.0 days, with a very clear dose-response relationship associated between the number of times HA courses and time to TKA. Secondly, there are certain populations of patients that have contraindications to the used of other conservative/pharmacological methods of treatment, and with the good safety profile of HA injections, could be a more viable long-term option for treatment. This group can also include patients who are not suitable for surgical intervention or opt not to undergo surgery for various reason. A third reason of importance is that TKA, although improving in

quality, only lasts a certain number of years, requiring a second, more-costly and risky revision surgery. There are certain factors such as younger and more active patients whom put more wear and tear on the prosthesis requiring earlier revision. (23) With the prolongation of the need for initial TKA this may reduce the likelihood of revision surgery later on, along with the associated surgical risks for the patient and cost to the health care system. There have been a few studies conducted looking at cost analysis of HA use for knee OA which showed beneficial cost- saving for the associated health care system. (24,25) These studies reported positive findings in regard to healthcare savings both in the short and long term. HA injections themselves do come at a cost, typically ranging between $300-$500 dollars Canadian, depending on the formulation. (26)

The studies also looked at various data that was not the specific reason for this review but were important nonetheless, such as effect based on gender, age, number of knees affected, radiological grading etc. which would be beneficial to look at specific sub-groups for treatment and its efficacy.

Limitations and Weaknesses

There are obvious limitations to the studies reviewed. First, the types of studies done were not of the highest quality. Cohort studies and case series sit low on the evidence-based medicine pyramid. Two of the studies lacked control groups completely and one was limited to 22 patients and no blinding. The retrospective records evaluation had an extremely large control group but again there were no blinding and placebo effects to be taken into account. The sample size of 183 in the study by Turajane Et. Al and 224 by Romero Et. Al. were also quite small with low statistical power, having a decreased chance of detecting a true effect. Another factor that plays importance is the actual type of HA used, which varied with each study, including things such as dosage guidelines and formulation/molecular weights. With this variability in the formulation in each study used, and the multiple different types of HA, there are

also no current guidelines regarding repeat administration of HA in that patient population that responded positively.

Conclusion

Based on the evidence provided by these studies, it is suggestive that the use of intra-articular HA vs. no treatment or failed conservative treatment is beneficial for patients with knee OA in prolonging the need for TKA. This is subjectively measured by decreasing pain and improving function along with quality of life, and objectively measured based on increased time to surgery. This benefit also includes patients whom have contraindications for TKA or other forms of conservative/pharmacological treatment. In order to confirm these results, more high quality studies should be performed with adequate controls and blinding of studies, which in turn could lead to further research regarding cost-savings within the Canadian healthcare system.

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