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Comparison of Non-NSAID Pain Management in the Treatment of Patients with Symptomatic Knee Osteoarthritis

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Abstract

Objective

To compare the efficacy of other modalities and interventions versus standard first-line therapy of nonsteroidal anti-inflammatory drugs for pain management in patients with symptomatic knee osteoarthritis

Methods

Perform literature reviews outlining patients suffering from Grade II or higher KOA using the Kellgren-Lawrence classification system and currently experiencing symptoms of pain, stiffness, and impaired physical functioning. Use data and results from various studies to compare improvement of symptoms from these modalities versus improvement of NSAIDs alone.

Results

Weight loss and physical activity should remain the mainstay of early osteoarthritis treatment to help slow disease progression and symptoms of KOA. Duloxetine has been shown to be non-inferior to treatment with NSAIDs and improved patient physical functioning and quality of life. Oral and intra-articular corticosteroids remain superior or equal in pain reduction but have a shorter duration of action and greater adverse reactions when taken long term. Ozone therapy is best used in post-operative pain management or severe flares of osteoarthritis to quickly reduce pain and inflammation, long term therapy is not recommended over NSAIDs. Glucosamine does not decrease pain related to KOA but when used concomitantly with NSAIDs can increase physical function, quality of life, and also slow disease progression. LP-PRP injections have greater efficacy and resulted

in lower WOMAC total scores at three, six, and twelve-month intervals when compared to ozone, hyaluronic acid, and corticosteroid injections. LP-PRP injections also have greater or equal efficacy of hyaluronic acid plus oral NSAIDs at one year. PRP therapy also has some evidence to suggest disease modifying potential. Hyaluronic acid injections resulted in less joint line tenderness and better physical functioning when compared to NSAID therapy alone, however, reduction in pain was not statistically significant. Prolotherapy was shown to be equally effective as PRP injections at pain reduction but requires serial injections. Benefit of prolotherapy is its safety profile and cost effectiveness. Finally, stem cell therapy resulted in lower WOMAC total scores when compared to hyaluronic acid injections. T2 MRI mapping indicates the ability of mesenchymal stem cells to regenerate cartilage and slow disease progression.

Conclusion

NSAIDs remain the most efficient means of pain reduction but do not result in statistically significant increases in physical function or quality of life. Hyaluronic acid can increase the patients physical functioning if used alone or in combination with NSAID therapy. Oral glucosamine sulfate, if taken daily, can reduce the progression of osteoarthritis but provides no pain relief if taken alone or without NSAIDs. Oral or intra-articular corticosteroids should be reserved for severe flares of pain in which the patient is unable to perform daily activities secondary to disability. Adverse reactions and possible further joint degeneration remain the biggest concern. Duloxetine should be considered in patients suffering chronic and refractory pain related to KOA and can be used in addition to NSAIDs to provide long term relief. Clinically the use of ozone

therapy is not relevant and pain reduction can be achieved in other modalities, use of ozone is best reserved for post-operative management to reduce inflammation. PRP injections are clinically relevant and provide statistically significant reductions in pain and disease progression. Use should be considered in patients who have failed other conservative KOA treatments. Finally, the use of mesenchymal stem cells does alter disease progression and reduce pain, but clinically its use is not relevant because the harvesting and cost are greater than other effective therapies currently. More evidence is needed to support its clinical use. In conclusion, alternative modalities should be considered if therapy with NSAIDs is not providing adequate reductions in pain or the goals of the patients are not being met. The aforementioned modalities are safe and effective adjuvant therapies to manage patients with symptomatic KOA.

Introduction

Osteoarthritis (OA) is the most common joint disorder in the United States, estimated to affect nearly 12% of adults ages 25-74.[1] Not all adults affected with osteoarthritis are symptomatic or seek treatment, leading to a slightly lower estimated prevalence. Regardless of actual prevalence, knee osteoarthritis (KOA) is the most frequent form OA and in 2004 accounted for 430,000 hospital discharges and roughly $14 billion in medical expenses.[2] According to Murphy L, Schwartz TA, Helmick CG, et al adults the lifetime risk of developing symptomatic KOA for both men and women is 40%-46% with little variation regarding race. However, this percentage increases to 56% if an adult suffers a significant knee injury during their lifetime and increases to an even greater 61% if the person is obese (Table 1, Appendix A).[2] Given the aging population and the increasingly sedentary lifestyle leading to diabetes, overweight, and obesity the projected incidence of KOA is estimated to continually rise and, therefore, cost the average US citizen more in medical expenses.

Understanding the etiology of KOA will further delineate the increasing likelihood of one suffering from joint disease. Osteoarthritis, specifically KOA, has a multifactorial etiology including age, sex, race, BMI, history of traumatic injury, physical activity, sedentary lifestyle, congenital, or acquired joint/ligamentous laxity. The etiologies and epidemiology of KOA demonstrate the importance of advancing treatment and modalities to help treat patients with symptomatic joint disease. First-line therapy for OA combines oral or topical non-steroidal anti-inflammatory drugs (NSAIDs) and non-pharmacologic management with moderate aerobic weight-bearing activity, physical therapy, weight loss, etc. Treatment with NSAIDs is feasible in a patient with a younger age or no comorbidities, however, KOA is a chronic progressive disease and tends to span decades and often requires combination pharmacological therapy. Therefore,

providers should be aware of and utilize other treatments and modalities to provide better pain relief and improved functioning to their patients. The purpose of the study is to compare the efficacy of other modalities and interventions versus standard first-line therapy of nonsteroidal anti-inflammatory drugs for pain management in patients with symptomatic knee osteoarthritis. The objectives demonstrating improved pain, functioning, and stiffness will be achieved using a variety of large studies on the topics of land-based or aquatic activity, corticosteroids, glucosamine sulfate, duloxetine, platelet-rich plasma (PRP) injections, hyaluronic acid injections, ozone therapy, dextrose prolotherapy, and mesenchymal stem cell injections.

Background

Land-Based and Aquatic Activity

Osteoarthritis is occasionally called "wear-and-tear" arthritis because the development of OA is typically seen in older patients who have placed continued stress on their joints throughout a lifetime. However, describing KOA as "wear-and-tear" can be significantly misleading for patients and possibly deter them from participating in physical activity. According to a 2012 study from the American College of Rheumatology physical activity is strongly recommended for symptomatic KOA, however, they expressed no preference for either land-based or aquatic exercise.[4] A common concern among patients is the possible worsening or progression of their joint disease if they continue performing daily activities or an exercise routine. The patient must understand the importance of physical activity for the positive systemic effects but also local joint health and protection. Exercise is known to have profitable trophic effects on periarticular bone and muscle in particular, and also tendon.[6] Similar effects are seen in the articular cartilage and many studies suggest that articular cartilage is mechano-adaptive; that is, the biosynthetic activity of chondrocytes is responsive to mechanical stimuli and can alter the

morphology and composition of cartilage.[6] Understanding the physiological of the effect on cartilage and bones, can it be used at monotherapy to treat patients with symptomatic KOA and provide equal relief compared to NSAIDs?

First, the notion of mild to moderate physical activity increases the likelihood of KOA must be eliminated. According to several retrospective and prospective cohort studies spanning roughly 18 years, there is no evidence routine land-based physical activity increases the likelihood or incidence of KOA in study participants. However, activities that placed the participants at increased risk for injury such as, heavy resistant weight training or competitive sports increased the incidence of KOA secondary to traumatic injuries alone.[8] Several other mechanical factors during physical activity can place an individual at risk for development or progression of KOA, but the act of exercise or activity is not the cause for this development (Figure 5, Appendix B).

One randomized clinical trial aimed to demonstrate the efficacy of physical activity when compared to routine care and symptomatic management. Kovar et al. enrolled 102 patients in either an eight-week supervised fitness and patient education program (n=51) or routine medical care (n=51). The eight-week program consisted of twenty-four 90-minute walking and education sessions which were designed and lead by registered physical therapists. These sessions occurred three times per week and included a light stretch, strengthening exercises, guest speakers on the medical aspects of osteoarthritis and exercise, group discussions, supportive encouragement, and about 30 minutes of walking. The researchers performed the walking sessions in the same hospital corridor with similar walking shoes, socks, and loose fit athletic clothing. The control group was instructed to perform similar physical activities unsupervised and was contacted weekly via telephone to discuss their activities of daily living. Functional improvement outcomes

were measured using a six-minute walking distance test and the Arthritis Impact Measurement Scale (AIMS). The AIMS arthritis pain subscale was used to assess pain and the medication subscale was used to assess medication use related to arthritis. The AIMS medication subscale is inversely related and the higher the number the less frequent the medication usage.

In the experiment group, following the interventions, walking distance improved an average of 70 meters, which reflects about an 18.4% increase from baseline. On the other hand, the control group decreased an average of 17 meters from baseline ($P < 0.001$). Furthermore, for the control group, the AIMS physical activity subscale reflected virtually no change. The study group demonstrated an improvement in 2.41 units from baseline, which is an improvement of about 39% and therefore statistically significant ($P < 0.001$). In summarization, the AIMS sub scores, on average, improved about 25% in the study group. Interestingly, the AIMS medication subscale increased by 0.84 units in the study group, which reflects the need for less rescue medication use.[42]

Land-based aerobic activity has been proven to decrease pain and disability, can aquatic exercise perform similarly? A large Cochrane review of thirteen studies comparing aquatic exercise and control demonstrates the effectiveness of aquatic exercise. The authors were studying the effects of interventions on pain, disability, and quality of life. The analysis of twelve out of the thirteen trials showed a statistically significant pain reduction (SMD −0.31, 95% C:−0.47 to −0.15). Disability, similarly, showed a statistically significant reduction following about 12 weeks of aquatic exercise (SMD −0.32, 95% CI −0.47 to −0.17). Ten out of the thirteen trials in the analysis also show a statistically significant improvement in quality of life (SMD −0.25, 95% CI −0.49 to −0.01).[43]

Oral and Intra-articular Corticosteroids

Pharmacologic intervention with corticosteroids in patients suffering from symptomatic KOA has been utilized clinically for several years. The mechanism of action for corticosteroid medications is similar to NSAIDs, however, corticosteroids are a more potent inhibitor of inflammation. Corticosteroids have a complex mechanism of action by acting on the nuclear steroid receptors to interrupt the inflammatory cascade on several levels. They reduce vascular permeability and inhibit accumulation of inflammatory cells, phagocytosis, production of neutrophil superoxide, metalloprotease, and metalloprotease activator, and prevent the synthesis and secretion of several inflammatory mediators such as prostaglandin and leukotrienes.[7] The prevention of prostaglandins and leukotrienes proves to provide relief for symptomatic KOA because these inflammatory mediators are directly involved in the patients' pain response. Several routes and dosages are used when administering corticosteroids and the most common in the treatment of KOA are oral or intra-articular, both will be discussed at length.

The benefits of oral corticosteroid therapy for symptomatic KOA are ease of access, cost, and route form. Corticosteroids tend to be easily accessible for both patients and providers and cost tends to be around $1 per pill.[10] The risks of oral corticosteroid therapy are numerous and must be taken into account. The risks are as follows and certainly not limited to fractures (most commonly vertebral), moon face or rubicundity, depression, gastrointestinal symptoms, gastric ulcers, tinnitus, psychosis, acute infections, diabetes, and hypertension. A prospective cohort study demonstrated the long-term adverse effects of continuous low-dose prednisolone on 122 patients for 10 years and found 31 patients suffered fractures, 5 experiences osteonecrosis, and 36 developed cataracts.[9] Conversely, low-dose prednisolone is not only highly effective for short-term therapy, but also significantly more effective than non-steroidal anti-inflammatory

drugs. (Table 2, Appendix A) A systematic review of the effect of low dose prednisolone after six months also found a significantly better effect of the drug than of placebo. Prednisolone also had a greater effect than non-steroidal anti-inflammatory drugs on joint tenderness (SMD = -0.63, 95% CI -1.16 to -0.11) and pain (SMD = -1.25, 95% CI -2.24 to -0.26). [9] Similar to NSAIDs, corticosteroids are used as rescue medication during flares or increases of KOA related pain and should not be used as long-term or prophylactic medication given the negative adverse effects. After interpreting the data, patients who can tolerate short "bursts" of oral corticosteroids during periods of increased pain due to KOA can see significant reductions in pain and improvement in joint line tenderness.

Intra-articular corticosteroid therapy has the same mechanism of action as oral therapy resulting in a reduction of pain and inflammation. The benefit of intra-articular infiltration involves less systemic absorption and therefore, less negative adverse reactions commonly seen with corticosteroid therapy. Typically larger joints receive a greater amount of injected corticosteroid and risk greater systemic absorption. The most common adverse reaction is seen in patients with diabetes, all with previously well controlled blood sugar levels, who received intra-articular corticosteroids concurrently had a transient increase in blood sugar levels, some as high as 300mg/dL.[11] A more potent inhibitor of cytokines and leukotrienes with less systemic absorption and possible side effects, why is this not first-line treatment for symptomatic KOA?

A randomized control study containing 70 participants with ages averaging 53 years old was performed to compare the efficacy of oral NSAIDs and intra-articular corticosteroid injections in the reduction of rheumatoid arthritis related knee pain. Participants were divided into two groups, one group receiving diclofenac 150mg and aceclofenac 200mg two times per day for 21 days. The other participants were designated into a steroid group and received three

administrations of either cortivazol 75mg or betamethasone 2mg at one-week intervals. All participants were monitored for another six weeks and the NSAID group had a greater improvement in pain, functioning, and stiffness (Table 3, Appendix A) from initiation until day 42 of the study.[12] Additionally, three limitations must be discussed in this study possibly leading to bias or ambiguity. The authors failed to report or document side effects from either treatment, participants in the NSAIDs group were roughly 13 years older on average, and the intra-articular steroid group had higher reported baseline pain and greater reported functional impairment than the NSAIDs participants.

These results suggest that a combination of both NSAIDs and intra-articular steroid treatments may be performed for optimal pain relief and functional improvement. For example, a patient regimen could be similar to a steroid infiltration on the first day followed by the treatment of NSAID two times daily until resolution up to 21 days. If the patient cannot tolerate the procedure of an intra-articular steroid injection or NSAIDs are contraindicated, oral prednisone may be another alternative but adverse reactions must be closely monitored. Furthermore, dual therapy with NSAIDs and steroids is contraindicated secondary to increased risk of gastrointestinal symptoms and ulceration.

Duloxetine

The mechanisms underlying the pain of osteoarthritis are chronic, progressive, and complex. There is evidence that central sensitization contributes to the chronic pain associated with KOA, and dysfunction of the descending pain inhibitory system contributes can contribute to the central sensitization. Duloxetine, a selective norepinephrine reuptake inhibitor (SNRI), typically used in depression and neuropathic pain, has shown some analgesic properties in pain related to KOA.[16, 17] The exact mechanism of action by which duloxetine inhibits pain is

unknown. Although, it is presumed to activate the descending pain inhibitory system in the dorsal spinal horn due to the effects of increasing serotonin and norepinephrine levels in the synaptic cleft of the spinal and supraspinal pathways.[17] NSAIDs have been proven effective in treating synovitis due to cartilage degeneration, however, central sensitization may prove to be an equal contributor to pain generation in KOA. Therefore duloxetine, in theory, may prove effective in treating central sensitization contributing to pain seen in chronic KOA.

A randomized, placebo-controlled study in Japan enrolled 353 participants with KOA to compare the efficacy of duloxetine versus placebo. The study group was further divided into subgroups pertaining to previous NSAID use three months prior to treatment initiation. Subgroup 1 had no prior NSAID use, subgroup 2 used NSAIDs less than 14 days per month, subgroup 3 used transdermal NSAIDs more than 14 days per month, and subgroup 4 used NSAIDs more than 14 days per month. Participants' pain was measured at baseline using the BPI 24-hour average pain scale. A secondary efficacy measurement was utilized by measuring the WOMAC pain, stiffness, and physical function subscales. The control group received a placebo while the study group received duloxetine 20mg capsules once daily for one week, two 20mg capsules for one week, and three 20mg capsules for 12 weeks. Both groups also received analgesic rescue medication which was permitted for up to three consecutive days and a cumulative total of 20 days. NSAIDs were permitted as rescue medications but the use of tramadol hydrochloride was forbidden.

During the 14 weeks treatment period, the study group receiving duloxetine required less rescue medication than the control group receiving placebo, regardless of previous NSAID usage Similarly, the BPI 24-hour average pain severity scale was lower at all times during the 14 weeks treatment period for the group receiving duloxetine in all subgroups (See figure 2, Appendix A).

Finally, WOMAC pain, stiffness, physical function, and total scores had greater reductions in all subgroups receiving duloxetine compared to placebo.[17] Given the results from the study, duloxetine may prove effective as an alternative treatment for pain related to KOA in patients. This is particularly beneficial in patients with cardiovascular or gastrointestinal comorbidities and a benefit-to-risk discussion is warranted. Enomoto et al. demonstrated duloxetine is more effective than a placebo at reducing pain, yet, is it more effective than NSAID therapy?

Myers et al. performed a meta-analysis of 32 randomized control studies demonstrating the efficacy of NSAIDs, duloxetine, and opioids in the management of KOA related pain. Studies were included only if the duration was greater than or equal to 12 weeks and the participant's pain was graded using the WOMAC total score. The outcome measure for the meta-analysis was a change in reported 12 weeks of WOMAC total scores compared to baseline WOMAC total scores. Estimated treatment effects of ibuprofen, naproxen, celecoxib, etoricoxib, tramadol, oxycodone, and hydromorphone were compared to placebo and compared to duloxetine were calculated with their 95% confidence intervals using the Bucher method of indirect comparison.[18] Using the frequentist analysis the results of the indirect comparison versus duloxetine showed duloxetine was superior to tramadol, celecoxib, and hydromorphone in reducing WOMAC scores from baseline (See Table 4, Appendix A). On the other hand, the authors also performed a Bayesian analysis using an indirect comparison versus duloxetine and adjusted for baseline WOMAC total scores which resulted in a probability duloxetine superiority over several other treatments (See Table 4, Appendix A). Duloxetine exhibited superiority over tramadol and hydromorphone with a probability of 1. Similarly, the probability duloxetine is superior to ibuprofen and celecoxib was 0.82 and 0.76 respectively. One notable limitation in the study was the number of randomized clinical trials used in the comparison of duloxetine over

oxycodone. The authors only used one study for adjusted baseline WOMAC total scores, in comparison to celecoxib, which had a total of 14 trials. Hydromorphone was shown inferior to duloxetine with 100% probability and potentially if more trials were used in the study, oxycodone would also be shown inferior.

The studies of Enomoto et al. and Myers et al. validate duloxetine superiority when compared to placebo. Myer et al. establish duloxetine is non-inferior to all other first-line medications in the management of KOA, except etoricoxib, and is more beneficial in reducing WOMAC total scores than hydromorphone and tramadol. Clinically this can be utilized by providers seeking safe and effective alternative treatments for chronic pain related to KOA.

Intra-articular Ozone (O_3) Injections

Oxygen-ozone solution can improve tissue oxygenation and inhibit inflammatory mediators mediated by the down-regulation of TNF_α and $TNFR_2$. Ozone therapy can also induce moderate-intensity oxidative stress and inhibit inflammatory responses. Ozone also has a relatively moderate analgesic effect through phosphodiesterase A_2 blockage.[19] Therapy with ozone first began in 1987 as a possible treatment for abscesses, acne, HIV, cerebral sclerosis, wound healing, and numerous other pathologies. Throughout the next several decades, ozone therapy has continually evolved and has evidence of anti-viral and anti-bacterial properties, reduce the activity of tumor cell suspensions from the breast and colon, and reduce abscess formation with irrigation.[23] More so, in the past decade, there has been increasing investment into ozone therapy for the symptomatic relief of pain related to KOA. Ozone injections are an effective and low-cost procedure to help symptoms. Is ozone therapy effective enough to limit or discontinue the use of NSAIDs?

A retrospective observational study evaluated 80 patients suffering from Kellgren-Lawrence Grade II or III symptomatic KOA who received intra-articular ozone therapy following arthroscopic debridement. The control group following arthroscopic surgery did not receive ozone injections and the study group received 20ml of 20mg/mL of ozone post-surgery. The participants were followed for 12 months and efficacy outcomes were measured using WOMAC total scores, Lequesne, and the VAS score at 6 weeks, 3 months, 6 months, and 12 months. It was observed that the VAS scores significantly decreased from 7.52 prior to treatment to 5.17 at the 12- months follow-up in the ozone group, whereas in the control group, the VAS scores decreased from 7.66 to 6.56 (Figure 3.2, Appendix B).[21] The Lequesne Index improved from 15.07 to 8.74 in the ozone group and from 14.26 to 10.08 in the control group at the 12-month follow-up (Figure 3.1. Appendix B).[21] Finally, the total WOMAC score improved to 41.19 from 70.43 in the ozone group, and 58.84 from 73.68 in the control group at the 12-month follow-up (Table 5, Appendix A).[21] Wang et al. demonstrate the efficacy of O_3 injections in the management of post-arthroscopic pain control compared to placebo. Clinically this is relevant because often times NSAIDs are withheld following orthopedic surgeries or fractures on the basis they may decrease boney healing.

Ozone injections have proven an effective alternative medication in the management of patients suffering from KOA related or post-operative pain, but is it superior to NSAIDs? An interventional study performed by Feng et al. aimed to evaluate the effect of intra-articular ozone in KOA related pain compared to taking oral celecoxib and glucosamine. The study enrolled 76 patients currently suffering Kellgren-Lawrence Grade II or III symptomatic KOA and randomly assigned them into two groups. The control group took oral celecoxib 200mg one time in the morning and glucosamine hydrochloride 240mg every morning, afternoon, and night for a total

of six weeks. The study group received 20ml of 20mg/mL ozone intra-articular two times per week for six weeks along with the same oral regimen of the control group. The randomly assigned groups were deemed to have no statistically significant difference in demographics, Lysholm scores, or baseline VAS scores prior to initiation, effectively ruling out bias. As previously mentioned, efficacy outcomes measured using the VAS score for pain and the Lysholm knee score for the functional ability of the knee.[22]

At the end of the six weeks, the pain score and the function of the knee between the two groups had no significant difference. However, the function improved quicker in the ozone plus celecoxib and glucosamine hydrochloride group compared to the control. The exact mechanism by which the pain resolved quicker is unknown but is believed to be due by the reduction of inflammation by both the oral anti-inflammation medicines and the ozone injections which have different mechanisms of action.[22] A determination for the efficacy of ozone injections over NSAIDs could not be concluded given the previous studies, conversely, intra-articular ozone injections are proven to decrease pain and increase function faster than NSAID therapy alone. Furthermore, intra-articular ozone therapy is more effective in pain reduction and physical function when compared to placebo.

Glucosamine Sulfate

Historically the treatment of osteoarthritis has centered around symptomatic relief of pain and improvement of stiffness and functional ability. Symptom modifying, typically NSAIDs, are the present prescription of choice for symptomatic OA. However, the search for a possible disease-modifying or biological agent has been the goal for several years, glucosamine sulfate appears to be the most readily available and promising. Glucosamine is the most fundamental building block required for the biosynthesis of the classes of compounds including glycolipids,

glycoproteins, hyaluronate, and proteoglycans. These compounds play an important role in the synthesis of cell membranes or linings, collagen, osteoid, and boney matrix. Finally, glucosamine is also required for the formation of lubricants and protective agents such as mucin and mucous secretion.[13, 14] Glucosamine sulfate is most commonly extracted from the shells of shellfish such as shrimps, crabs, and lobsters, and must be avoided in patients with allergies to these animals.

As previously mentioned, this biological agent is readily available and shows the most promise for a possible disease-modifying OA agent, nevertheless, does it produce enough symptomatic relief for patients to warrant use over NSAIDs or limit the need for NSAIDs? A 2012 clinical study to determine the efficacy of glucosamine sulfate alone versus glucosamine sulfate in addition to NSAIDs was performed to help answer this question. The study enrolled 82 patients suffering from mild to moderate KOA, identified radiographically using the Kellgren-Lawrence scale, and were divided into group A and group B. Group A consisted of 43 patients who were treated with 500mg glucosamine sulfate three times per day. Group B consisted of 39 patients and was treated with 500mg glucosamine sulfate three times per day plus either Ibuprofen or Piroxicam once daily. Both groups would be reassessed every 30 days for 3 months using the WOMAC pain, stiffness, and function scores in addition to the VAS score. The mean WOMAC total score of group A on week zero was 47.65 ± 3.69 and after four weeks increased to 48.09 ± 2.23. However, at 12 weeks and completion of the trial, the mean WOMAC total score for group A was 30.58 ± 1.41 with the mean difference being 17.06 ± 4.54. Using the P-value ($P < 0.01$), the mean score decrease was statistically highly significant. On the other hand, the mean WOMAC total score of group B was 50.76 ± 3.88 on week zero and decreased to 39.64 ± 4.31 after four weeks. After 12 weeks, the mean WOMAC total score was 14.79 ± 3.16

with the mean difference of 35.97 ± 4.24. The result of group B revealed that the mean score decrease was statistically highly significant (P < 0. 01). Continuing to use the P-value and comparing the results of group A and B revealed a significant difference between the two groups (P < 0.01). Similar to the WOMAC, the secondary efficacy variable using the VAS score results in a higher mean difference in group B following the conclusion of the study at 12 weeks.[15]

Interpreting the data from Selvan et al. is apparent in combination therapy with NSAIDs, and glucosamine sulfate resulted in highly significant reductions in pain and stiffness and increased physical functioning. Unfortunately, the study does not completely answer whether glucosamine sulfate alone is more effective than NSAIDs alone. Clinically the study remains relevant by demonstrating the efficacy of combination therapy with NSAIDs and glucosamine sulfate in maintaining and improving patient quality of life.

Glucosamine sulfate alone or in combination with NSAIDs can significantly reduce symptoms of KOA, but can it slow the progression of OA and possibly reduce the need for future NSAID usage? Pavelká et al. performed a three-year randomized, placebo-controlled, double-blind study aimed at determining the efficacy of glucosamine sulfate in limiting the progression of joint structure and symptom changes in KOA. The study enrolled 200 patients and was randomized to receive either placebo or 1500mg glucosamine sulfate once a day. Radiographs were taken at enrollment and after 1, 2, and 3 years of treatment by the same technician using the same x-ray machine and approach. The study utilized anteroposterior weight-bearing plain films with the participant's heels and toe together with the knees in full extension. The primary outcome measure was represented by joint space change in the narrowest medial compartment of the tibiofemoral joint. Placebo-controlled participants demonstrated progressive joint space narrowing of -0.19mm (95% CI, -0.29 to -0.09mm) after 3 years. The glucosamine sulfate study

group experienced no average change (0.04mm, 95% CI, -0.06 to 0.14mm). See Figure 1 in Appendix B for more year-to-year detail. The difference between the two groups (P = .001) is statistically highly significant. Results of the study demonstrated long term therapy with 1500mg glucosamine sulfate slowed KOA disease progression utilizing joint space narrowing.[16]

The results of both Pavelká et al. and Selvan et al. demonstrate glucosamine sulfate can be used to slow disease progression for patients with diagnosable mild to moderate KOA and can be used in combination with NSAIDs to increase symptomatic relief of pain and stiffness. However, KOA is a chronic and progressive condition and the limitation of the studies is the lack of substantial time of monitoring. Furthermore, the studies of Pavelká et al. cannot fully determine the efficacy of glucosamine sulfate use prophylactically prior to the diagnosis or symptoms of KOA.

Intra-articular Platelet Rich Plasma (PRP) Injections

Intra-articular platelet-rich plasma injections have been shown to decrease chondrocyte apoptosis, increase proteoglycans in the articular cartilage, and prevent against OA progression. The mechanism of action within the joint is unknown but is thought to provide relief by delivering a broad spectrum of growth factors such as insulin-like growth factor, transforming growth factor b-I, platelet-derived growth factor, etc. It is also thought to deliver other active molecules such as cytokines, chemokines, arachidonic acid metabolites, extracellular matrix proteins, nucleotides, ascorbic acid to the joint.[7] Platelet-rich plasma (PRP) is prepared using autologous human plasma with an increased platelet concentration produced by centrifuging a larger volume of a patient's blood. Preparations are further categorized into leukocyte-rich PRP (LR-PRP) preparations, having leukocyte concentration above baseline, and leukocyte-poor PRP (LP-PRP) preparations, having a leukocyte concentration below the baseline.[24] Similar to

glucosamine sulfate, PRP injections are aimed at reducing KOA symptoms and act as a disease-modifying or biological drug to help prevent the progression of KOA. Currently, according to the American College of Rheumatology 2019 Osteoarthritis Guidelines, the use of PRP injections for the treatment of knee and hip osteoarthritis is strongly recommended against.[3] Contrarily, the American Academy of Orthopaedic Surgeons Clinical Practice Guidelines consortium concluded that they "could not recommend for or against PRP in the treatment of symptomatic knee osteoarthritis."[25] Inconsistent recommendations can cause provider and patient confusion regarding alternative treatments or modalities. Can PRP injection be proven effective to reduce pain related to symptomatic KOA or slow disease progression, therefore, limiting the use of NSAIDs?

A systemic review by Shen et al. with 14 randomized control trials and comprising a total of 1423 participants was performed to outline the efficacy of PRP injections compared to other KOA treatments.[26] All studies were required to include at least one control group treated with intra-articular hyaluronic acid, ozone, or corticosteroid injections. Primary efficacy outcomes were measured using the WOMAC pain, physical function, and total scores at intervals of three, six, and twelve months. Studies were not excluded based on the preparation of either LR-PRP or LP-PRP.

WOMAC pain scores at three months were reported by several studies and were found to be statistically significant and in favoring PRP injections versus control. Similar results were demonstrated at both six- and twelve-month intervals. WOMAC physical function and total scores at three, six, and twelve-month intervals were also found to be statistically significant and in favor of PRP injections over intra-articular ozone, hyaluronic acid, and corticosteroid injections. (Table 6.1-6.3, Appendix A) Only ten studies recorded adverse effects and there was

found to be no statistically significant difference between PRP injections versus the other intra-articular injection's adverse effects. Non-specific adverse effects were recorded and included pain, stiffness, syncope, dizziness, headache, nausea, gastritis, sweating, and tachycardia. All adverse effects were monitored and resolved within a few days. Given the results of Shen et al. intra-articular PRP injections are more effective than saline placebo, corticosteroid, ozone, and hyaluronic acid injections at three, six, and twelve-month reporting.[26]

Another randomized control trial performed by Buendía-López et al. aimed at comparing the efficacy of PRP injections versus intra-articular hyaluronic acid and oral NSAIDs in 106 participants.[27] The control group received 60mg etoricoxib to be taken concomitantly with omeprazole for 52 weeks. The hyaluronic acid group received a single intra-articular injection of Durolane©, a high molecular weight hyaluronic acid preparation (60mg/2mL). Lastly, the PRP group received a 5mL injection of LP-PRP prepared from 60 ml of peripheral blood extracted by venipuncture of the antecubital vein. All participants were evaluated before initiation, at six months, and twelve months. Efficacy outcomes were measured by a 20% decrease in WOMAC pain, stiffness, and physical function scores. Secondary measures included the VAS score, x-ray, and MRI progression. There was no statistically significant difference between the three groups in either baseline measurements.

During the 6-month evaluation and regarding the primary outcome measures (WOMAC pain, stiffness, and physical function), the rate of response to PRP was 30 percentage points higher than the rate of response of NSAIDs (95% CI 26–32; $P < 0.05$). Secondary outcome measures had similar results with the VAS being 30 percentage points higher than NSAIDs. (95% CI 27-32). At the 12-month evaluation, the rate of responses between PRP and NSAIDs remained nearly identical to results from the 6-month evaluation for both primary and secondary

outcomes (Table 7.1-7.2, Appendix A). However, when comparing the PRP, HA, and NSAID groups in reference to the cartilage thickness reduction or joint space narrowing, there was no statistically significant difference. Therefore, it can be concluded PRP injections are effective in reducing WOMAC pain, stiffness, physical function, and total scores better than hyaluronic acid and oral NSAIDs at 12-month evaluations. On the other hand, the results from the study demonstrate PRP injections may not have a positive effect on the progression of KOA and cannot be used as a prophylactic measure to reduce joint space narrowing or cartilage degeneration.[27]

Now that the efficacy of PRP injections over other treatments has been established is there a difference in results based on the preparation? As previously mentioned, there are currently two preparations available for PRP injections, leukocyte-poor (LP-PRP), and leukocyte-rich (LR-PRP). During the study of the effect of PRP injections in rabbit tendons, high concentrations of white blood cells (LR-PRP) were shown to increase the expression of catabolic cascades and inflammatory markers such as interleukin-1 and tumor necrosis factor-alpha, causing cell death.[29] On this evidence alone it would seem injections with less white blood cells would be more suitable for medical or clinical interventions.

Riboh et al. aimed to demonstrate a difference between the PRP preparations by outlining improvements of pain and comparing adverse effects. The authors compared data from six randomized control studies and three prospective studies. First, they compared reductions in WOMAC pain, stiffness, and physical function scores in PRP injections versus hyaluronic acid and placebo injections. They further divided the results by comparing studies using either LR-PRP or LP-PRP and which preparation provided the greatest reduction in WOMAC sub-scores.

Finally, the authors compared adverse effects between both preparations of PRP injections and hyaluronic acid injections.

Injection of LP-PRP resulted in significantly better WOMAC scores than did injection of hyaluronic acid (mean difference, –21.14; 95% CI, –39.63 to –2.65) or placebo (mean difference, –17.84; 95% CI, –34.95 to –0.73). No such difference was observed with LR-PRP (mean difference, –14.28; 95% CI, –44.80 to 16.25).[29] The incidence of local adverse reactions was greater in PRP injections than hyaluronic acid (odds ratio, 5.63; 95% CI, 1.38-22.90), but there was surprisingly no difference in local adverse effects based on leukocyte concentration.[29]

Intra-articular Hyaluronic Acid Injections

Hyaluronic acid is a naturally occurring glycosaminoglycan found in the synovial fluid and cartilage matrix. The pathogenesis of OA causes a decrease in both molecular weight and concentration of hyaluronic acid in the synovial joint. It is thought that hyaluronic acid temporarily restores the lubricating and shock-absorbing effects of synovial fluid and might also have disease-modifying effects, such as reduction of synovial inflammation, protection against cartilage erosion, and promotion of intra-articular hyaluronic acid production.[7] Clinically it is derived from the combs of roosters or via in vitro bacterial fermentation. Benefits of treatment with hyaluronic acid include a positive safety profile and a non-invasive procedure. However, hyaluronic acid tends to be very expensive, health insurance coverage tends to be difficult to acquire, and certain manufacturers or providers perform serial injections once weekly for three weeks, which can be more expensive and time consuming for the patient. As noted earlier, documented adverse effects for hyaluronate sodium therapy typically remain local such as injection site irritation. Contrasting the adverse effects alone, hyaluronate sodium therapy may seem more appealing to patients than NSAIDs, but is it equally or more effective?

A randomized, double-blind, placebo-controlled trial performed by Petrella et al. was conducted to determine the efficacy of hyaluronate sodium versus NSAIDs. The researchers used subjective measures of pain, stiffness, disability at rest, and following walking or stepping activities of 120 patients. These participants were divided into four randomized groups each unaware of the treatment they were receiving. Group 1 received 2mL of hyaluronate sodium intra-articular at a concentration of 10mg/mL and oral placebo (100mg lactose). Group 2 received diclofenac 75mg and misoprostol 200mg and hyaluronate sodium intra-articular. Group 3 was assigned diclofenac 75mg and placebo. Finally, group 4 was assigned oral lactose and intra-articular saline as a placebo. The aforementioned measures were used to determine the efficacy of treatments along with physical function testing. The physical function was determined in two ways, first, the subjective WOMAC stiffness and physical disability sub-scores, second, a self-paced walking and self-paced stepping test were administered. The self-paced walking test consisted of a 40-meter walk at a comfortable or "normal" pace chosen by the participant. The self-paced stepping test consisted of stepping at a comfortable or "normal" pace up and down 9.5-inch steps 20 times.

Self-reported and subjective pain using the WOMAC scores were similar at baseline in all four groups. Groups one, two, and three showed a significant decrease in pain recorded on the WOMAC global score at the four-week interval. Pain scores for groups one and three remained the same as week four until termination of the study. However, group 2 demonstrated a statistically significant improvement in pain ($P = 0.005$). Similarly, groups one, two, and three, showed statistically significant ($P < 0.05$) improved in physical functioning at week four but remained unchanged in group three until termination. Therefore groups one and three showed further significant improvement ($P < 0.05$) in week four until completion of the study. Finally, the

results of the self-paced walking and stepping testing demonstrated similar results. Interestingly, pain during rest and following the self-paced walking test was significantly ($P < 0.05$) less in all four groups following the four weeks follow up, while only groups one through three showed improvement in the self-paced stepping at four weeks. Furthermore, there was no significant difference or improvement in reported pain following the self-paced walking test in all four groups after week four until termination. Interestingly, at week 12, group one had significantly lower ($P < 0.05$) improved pain following the self-paced stepping test, group two remained unchanged, and groups three and four had significantly ($P < 0.05$) higher pain scores.[38]

Another double-blind, randomized clinical trial aimed to determine the efficacy of hyaluronic acid versus NSAIDs performed by Adams et al. reached a similar conclusion. They divided 102 patients into three groups; group one received oral NSAIDS only, group two received intra-articular hylan GF-20 only, and group three received both oral NSAIDs and intra-articular hylan GF-20. Participants were graded using the WOMAC and VAS scores and followed for a total of 26 weeks. The results of the study support the use of hylan GF-20 or hyaluronic acid for symptomatic treatment and management of patients diagnosed with KOA. Furthermore, the results of Adams et al. support the hypothesis that treatment with hyaluronic acid alone is at least as effective with NSAIDs alone.[39]

Intra-articular Dextrose Prolotherapy

Prolotherapy involves the injection of a hypertonic irritant solution, usually a combination of normal saline and dextrose, into damaged tissue such as cartilage to encourage cell proliferation. The exact mechanism of action is unknown; however, the current belief is the solution creates a hyperosmolar environment and the irritant induces inflammatory cascades and stimulates the local healing of cells and release of platelet-derived growth factor.[37] As

previously mentioned, the solution typically contains dextrose, normal saline, and a local anesthetic administered before or during the procedure. Prolotherapy can be very appealing due to the large availability of these medications or solutes. On the other hand, when discussing prolotherapy with possible patients who may benefit, understanding the need for routine or serial injections must be achieved. The usual regimen includes more than one injection monthly, most often patients receive upwards of three or four per month. With the need for serial injections, is prolotherapy feasible for patients when oral medications or other treatments require less commitment? A quality improvement project performed by Rabago et al. aimed to answer this question by inviting patients suffering from symptomatic KOA whose insurance plan covered prolotherapy injection to a primary care office to receive these injections. Feasibility was measured by the acceptance rate of the invitation and acceptability was measured by patient adherence and satisfaction with three or more prolotherapy injections. In total, thirty-nine patients were invited to receive the injections, eleven responded and only seven received three or more injections. The authors believed an acceptance rate of 18% was satisfactory and concluded prolotherapy is a feasible option to be performed in an outpatient or primary care clinical setting. [36] Prolotherapy has been proven to be feasible and cost-efficient, however, is it effective in the symptomatic management of KOA?

The efficacy of PRP has been discussed previously and a randomized, double-blind, clinical study aimed at comparing prolotherapy with PRP. 42 patients were enrolled in the study, one group was to receive a 7mL PRP injection as a control (n=21) and the study group (n=21) was to receive a 7mL 25% dextrose injection. The participants were admitted into the operating room and knee symptoms were measured using the WOMAC scores at baseline. Each patient received the same routine monitoring processes including blood pressure, heart rate, ECG, and a

20mL blood sample. The 20mL blood sample was then placed in a centrifuge and the separated plasma was prepared for the 7mL PRP injection in the control group. Using ultrasound guidance and the anterolateral approach either the 7mL PRP or 7mL dextrose was injected intra-articular, neither the provider nor the participant were aware of the contents. The same procedure was then repeated one month later for all patients.

Before initiation of treatment, there was no statistical significance in the baseline WOMAC scores or demographics between the control and study group. The results of the study show a statistically significant decrease in pain, stiffness, and physical limitation subscores in all follow-up intervals for both PRP and prolotherapy injections. A similar pattern of relief was noticed in both treatments in which, subscores were gradually and progressively decreasing for the first two months and by the six months began to slowly increase once again. (Table 8.1-8.3, Appendix A).[33] Comparably the WOMAC total scores for both groups followed the same pattern of improvement (Table 8.4, Appendix A).[33] While the statistical improvement in all efficacy outcomes during the follow-up intervals for both injections was demonstrated, according to the results PRP injection provides more improvement and longer when compared to prolotherapy.[33]

Intra-articular Mesenchymal Stem Cell Injections

Therapy to help improve the patient's symptoms and hinder the progression of a specific disease has been the goal of research for years, not only related to osteoarthritis but all pathologies. One promising therapy is the use of stem cells in both symptomatic resolution and regenerative medicine. Stem cells are a difficult discussion due to ethical challenges in obtaining cells and the advanced scientific knowledge required to understand the origin and complex differentiation potential. Speaking generally there are typically five classes or potentials for stem

cells, omnipotent, pluripotent, multipotent, oligopotent, and unipotent. Omnipotent, occasionally called totipotent, has the most differentiation potential, these cells can develop in embryonic and extra-embryonic tissues. The most important characteristic of omnipotent is the ability to differentiate and generate a fully functional living organism and are most recognizable as a zygote. Pluripotent stem cells are typically derived from embryonic stem cells or induced pluripotent stem cells (iPS cells). These cells can self-renew and differentiate into three germ layers comprising human tissues and organs; ectoderm, endoderm, and mesoderm. Multipotent stem cells, similar to pluripotent, also can self-renew and differentiate into specific cell types. The most common example and the focus in osteoarthritis treatment are mesenchymal stem cells (MSC), which can differentiate into osteoblasts, myocytes, adipocytes, and chondrocytes. One benefit of MSC is the ability to harvest these types of cells ethically, safely, and without advanced procedures. Oligopotent stem cells also can self-renew and differentiate but are very limited in ability and typically only differentiate into closely related types. Hematopoietic stem cells (HSC) are the most common example of oligopotent stem cells; these cells are derived from mesoderm and differentiate into other blood cell types. Finally, unipotent stem cells are the least potent and most limited stem cell type. While they can self-renew and differentiate, they are unidirectional in their differentiation capacity and only differentiate into a single cell type.[30]

Multipotent stem cells, particularly multipotent stem cells, have been the interest of researchers for several years aiming to discover osteoarthritis treatments with potential restorative or regenerative mechanisms. In recent years, MSCs have been the most promising due to their highly available origin in the body and the potent ability to self-renew and differentiate. The most important and useful characteristic for MSCs is the non-immunogenic profiles. In other words, allogenic transplantation can be performed without the need for

immunosuppression. The three most common origins of MSCs used in research are derived from adipose tissue, bone marrow, and umbilical cord.[31] Adipose-derived stem cells are derived from the stromal vascular fraction (SVF) in the subcutaneous tissues. They are plastic adherent and possess adipogenic, osteogenic, chondrogenic, myogenic, cardiogenic, and neurogenic potential in vitro.[31] As the name suggests, bone marrow-derived stems cells originate in the bone marrow and are thus harvested from this source. Bone marrow harvesting is considered the most invasive and painful procedure to harvest MSCs and requires general anesthesia plus several days for hospital care. Finally, umbilical cord-derived stem cells can be isolated from several different parts of the cord including, Wharton's Jelly, cord lining, and peri-vascular region. However, almost studies used MSCs that were derived from cord blood and Wharton's jelly.[31] Benefits and risks will not be discussed at length for each of these stem cells, regardless, the basic harvesting techniques and location must be understood before proceeding to discuss medical benefits in regenerative osteoarthritis treatment.

In a randomized control study performed by Vega et al. mesenchymal stem cells were compared to hyaluronic acid in participants with symptomatic KOA. 30 participants who previously failed other conservative managements were selected and placed into two groups, one group received intra-articular hyaluronic acid injections and the other group received allogenic bone marrow mesenchymal stem cell therapy by intra-articular injection of $40x10^6$ cells. Outcomes were followed for one year using the VAS score, WOMAC score, and Lequesne functional index. Also, MRI studies using T2 mapping were performed at baseline, six months, and one year to evaluate for articular cartilage quality using the poor cartilage index (PCI).

Comparing the control versus experimental groups VAS scores and WOMAC sub-scores at the six months and one year follow up, both groups experienced a consistent reduction in

scores. However, the MSC group experienced a statistically significant change in both VAS and WOMAC sub-scores at the aforementioned follow-ups (Figure 4.2, Appendix B).[32] The WOMAC general and Lequesne scores changed consistently for both groups, with significant decreases at six months and one year in the experimental group and no statistically significant change in the control group (Figure 4.1, Appendix B).[32] Similarly, the T2 mapping on MRI showed a decrease in the PCI for both groups, but the decrease was not statistically significant in the control group, while at the one year follow up it reached significance ($P<0.05$) in the MSC group.[32] The results validate the safety of allogeneic MSCs while simultaneously providing indications for their efficacy in treating osteoarthritis compared to other conventional KOA treatments. Furthermore, allogenic MSC treatment is shown to aid in cartilage repair and regeneration, possibly decreasing symptoms and progression related to KOA.

Conclusion

NSAID therapy has been the mainstay of osteoarthritis treatment because the goal of therapy is reducing pain and therefore improving physical functioning and quality of life. However, treatment with oral and topical NSAIDs are effective with pain management but no consistent long-term improvement of physical function with the use of NSAIDs alone has been reported.[38] Along with no improvement of physical function, there is a multitude of adverse effects of NSAIDs such as gastrointestinal complaints, ulcerations, cardiovascular complications, and renal clearance restrictions which can all limit their use in the older population. If modest pain reduction is the only goal NSAIDs can achieve, then alternative treatments are not only recommended but should be required for patients to improve their physical functioning and quality of life.

The effectiveness of land-based or aquatic exercise has been studied and proven in numerous studies. The magnitude of the pain relief, about 25%[42], would be considered small, but comparable to estimates reported for non-steroidal anti-inflammatory drugs.[41] Nonetheless, exercise will statistically and subjectively improve physical function and quality of life.[40-43] Another advantage physical activity has over NSAIDs, is the ability to possibly limit disease progression or prevent osteoarthritis. During gait, body weight is transferred onto the knee with substantial leverage, so that each additional kilogram of body mass increases the compressive load over the knee by roughly four kg.[40] For example, if a patient safely lost ten pounds, the compressive load on their knees would be reduced by roughly 40 pounds. Moderate weight loss, 5% of total body weight or intensive weight loss, 10% of total body weight, in older overweight and obese adults with KOA has positive effects on clinical and mechanistic outcomes, with a clear dose-response effect.[5] Land-based and aquatic physical therapy should be performed at least three times per week for prevention and treatment of osteoarthritis, in turn, this will decrease disease progression and limit the need for NSAID treatment.[40-43]

Oral and intra-articular corticosteroids are more potent inhibitors of inflammatory mediators and their efficacy for osteoarthritis has been clinically proven. In a 2019 foundation guideline, the American College of Rheumatology strongly recommends the use of intra-articular corticosteroids for the treatment of both hip and knee osteoarthritis.[3] According to Gotzsche et al., oral prednisone bursts are more effective at reducing pain with activity and joint line tenderness.[9] However, extended daily therapy for symptomatic treatment is not feasible due to the safety profile and adverse effects. Therefore, oral corticosteroid therapy can be helpful in patients suffering from advanced osteoarthritis with severe pain and tenderness or symptomatic osteoarthritis affecting several joints. Intra-articular corticosteroid injections appear to have a

better safety profile with less systemic adverse effects but a less than an ideal reduction in pain. According to the studies of Dieu-Donné et al., intra-articular corticosteroids have a better reduction in pain and physical improvement compared to NSAIDs but their efficacy is brief.[12] Thus, the clinic use of intra-articular corticosteroids may be reserved best for patients whose pain is not well controlled with daily physical activity and oral/topical NSAIDs. Additionally, the regimen appearing to provide the most relief is an intra-articular corticosteroid injection followed by as needed per day oral NSAIDs.[12]

For patients not willing to receive an intra-articular injection but still longing to pain relief due to their KOA, duloxetine has proven its efficacy as an alternative or additional treatment.[17-18] As previously discussed, central sensitization may prove to be an equal contributor to pain generation in KOA, and treatment with duloxetine alters this pathway. While selective serotonin and norepinephrine reuptake inhibitors have numerous adverse effects, they are typically well handled and can help reduce symptoms related to KOA. Regardless of prior treatments, the use of duloxetine will reduce pain and limit the need for rescue medications such as NSAIDs or tramadol.[17] Flares of pain related to KOA and synovitis can be reduced using NSAIDs while adjuvant use of daily duloxetine will help reduce the secondary pain pathway, resulting in an optimal reduction in pain. Similarly, Myers et al. outlined the efficacy of duloxetine compared to other oral daily and rescue medications. Duloxetine is clinically more effective than tramadol, celecoxib, hydromorphone, and oxycodone and should be conditionally recommended for symptomatic KOA.[3,18]

Due to allergic sensitivities, contraindications, or other comorbidities, NSAIDs may be restricted or limited in certain patient populations suffering from symptomatic KOA. Ozone therapy is a safe and low-cost procedure proven to be effective in reducing pain related to KOA

and post-arthroscopic procedures.[19-23] Wang et al. demonstrated the efficacy of intra-articular ozone versus placebo following an arthroscopic debridement secondary to symptomatic KOA. After 12 weeks patients who received intra-articular ozone had reduced pain and disability and increased functional ability. Ozone therapy should not be the only medication used for orthopedic related post-operative pain management; however, it can be used concomitantly with other measures if needed. Additionally, ozone therapy can result in faster pain relief and functional improvement than NSAIDs for a short period.[22] The use of intra-articular ozone can be used to help decrease post-procedural pain or severe flares of KOA related pain, but long-term efficacy is non-superior to NSAIDs.[19-23]

KOA is a chronic and progressive disease; therefore much effort is being placed in regenerative and restorative medicine. Glucosamine sulfate appears to be the most cost-effective disease-modifying drug available today. Unfortunately, glucosamine sulfate does very little in the management of pain related to osteoarthritis and should not be used in this manner. Selvan et al. demonstrated the use of glucosamine sulfate and NSAIDs is more effective at reducing WOMAC total scores than NSAID use alone.[15] Daily use of glucosamine sulfate has been proven to slow the progression of mild to moderate KOA and therefore possibly limit the need for further interventions and medications.[15-16] Despite the extensive studies demonstrating the efficacy of glucosamine in KOA, the American College of Rheumatology strongly recommends against the use.[3]

The use of LR-PRP and LP-PRP has numerous studies and analyses demonstrating its efficacy in pain reduction. Improving the quality of life, and possibly altering disease progression of KOA. Surprisingly, according to the American College of Rheumatology 2019 Osteoarthritis Guidelines, the use of PRP injections for the treatment of knee and hip

osteoarthritis is strongly recommended against.[3] On the other hand, intra-articular corticosteroids are strongly recommended for KOA. However, according to the meta-analysis of Shen et al., PRP therapy reduced WOMAC total scores better than intra-articular ozone, hyaluronic acid, and corticosteroids, at three, six, and twelve months.[26] Likewise, the adverse reactions are mostly limited to local injection reactions rather than the multitude of corticosteroids. If an injection performs better compared to standard therapy and with less adverse reactions, this therapy should be recommended or attempted in patients with continued symptomatic KOA.[24-29]

One of the most common complaints from patients suffering symptomatic KOA is the pain or joint line tenderness during and following activity. NSAIDs can decrease pain before activity if taken appropriately concerning time and duration. They also are effective and decreasing post-activity pain, but dosing restrictions typically limit usage before and after activity consumption. Therefore, hyaluronic acid may be more beneficial in patients seeking to remain physically active after a diagnosis of KOA has been made. It seems hyaluronate sodium therapy may show greater efficacy for activity-related pain and improvement of performance than NSAIDs or exercise therapy alone.[39] Not only may they be more effective but there is no daily or multiple times daily consumption requirements, making hyaluronic acid effective, efficient, and convenient. Hyaluronic acid increased functional ability in patients performing walking and stepping exercises, allowing them to walk farther and faster when compared to NSAIDs.[38] Given the data, treatment in patients with early symptomatic KOA may benefit from intra-articular hyaluronic acid treatments to maintain pain control and functional ability.[38-39]

Hypertonic solutions typically containing dextrose have been used in orthopedics for chronic tendinosis, muscle pain, or joint pain over the last several years. The mechanism of

action is not well established but it has shown promise in reducing pain related to osteoarthritis. According to Hung et al., prolotherapy is almost as equally effective as PRP, it is cheaper and can be covered by health insurance plans.[37] Prolotherapy does require serial injections to be performed weekly but patients are more likely and willing to participate if there is evidence of success and the treatment is cheaper than other alternatives.[36] The use of prolotherapy has been deemed not recommended by the American College of Rheumatology, however, the effectiveness has been demonstrated, and the treatment boasts an excellent safety profile.[3,37]

Mesenchymal stem cell therapy with the use of adipose stem cells is the new and emerging therapy for symptomatic KOA. While this therapy is strongly recommended against by the American College of Rheumatology, there is much evidence to support its use.[3,31,32,34,35] Compared to the control group, the MSC group experienced a statistically significant change in both VAS and WOMAC sub-scores and improved Lequesne at the one year follow up.[32] Allogenic MSC therapy has been shown to aid in cartilage repair by evidence of T2 mapping at serial follow-ups.[32] According to the studies of Vega et al. MSC therapy was proven more effective than intra-articular hyaluronic acid injections at recommended follow-ups.[32] Finally, there is clinical data to support the use of MSCs in patients suffering from hip, ankle, and knee osteoarthritis for both symptomatic management and possible disease modification.[35]

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Appendix A

Tables

Table 1
Lifetime risk probabilities and 95% CIs for symptomatic knee OA, stratified and overall*

	Lifetime risk percentage (95% CI)
Stratified	
Men	39.8 (32.2–47.3)
Women	46.8 (41.2–52.5)
Race	
Black	50.1 (41.8–58.4)
White	43.8 (38.4–49.1)
Education†	
Less than high school	43.5 (37.5–49.5)
High school completed	51.9 (42.2–61.6)
Greater than high school	34.8 (25.8–43.8)
BMI, kg/m^2†	
<25 (underweight and normal weight)	30.2 (23.0–37.4)‡
25–<30 (overweight)	46.9 (39.3–54.5)§
≥30 (obese)	60.5 (53.0–68.1)
History of knee injury†	
No	42.3 (37.2–47.4)
Yes	56.8 (48.4–65.2)¶
Overall	44.7 (40.0–49.3)

* Symptomatic knee OA is Kellgren/Lawrence scale radiographic grade ≥2. 95% CI = 95% confidence interval; OA = osteoarthritis; BMI = body mass index.
† Education, BMI, and history of knee injury in these models were time dependent (e.g., education of participants at each time point was analyzed).
‡ Comparison of lifetime risk, normal weight and obese, $P < 0.0001$.
§ Comparison of lifetime risk, overweight and obese, $P = 0.01$.
¶ Comparison of lifetime risk, history of knee injury (no and yes), $P = 0.002$.

Table 2
Comparison of Oral Corticosteroids vs NSAIDs

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Joint tenderness	4	144	Std. Mean Difference (IV, Random, 95% CI)	-0.63 [-1.16, -0.11]
1.1 Allocation concealment unclear	4	144	Std. Mean Difference (IV, Random, 95% CI)	-0.63 [-1.16, -0.11]
2 Pain	3	153	Std. Mean Difference (IV, Random, 95% CI)	-1.25 [-2.24, -0.26]
2.1 Allocation concealment unclear	3	153	Std. Mean Difference (IV, Random, 95% CI)	-1.25 [-2.24, -0.26]
3 Grip strength	4	142	Std. Mean Difference (IV, Random, 95% CI)	0.31 [-0.02, 0.64]
3.1 Allocation concealment unclear	4	142	Std. Mean Difference (IV, Random, 95% CI)	0.31 [-0.02, 0.64]

Table 3
Efficacy of NSAIDs vs intra-articular steroids on pain and Lequesne index from initiation until day 42

	NSAIDs (n = 35)		SIAI (n = 35)		Probability
	D0	D42	D0	D42	
VAS average	50.5	6.7	63.9	17.8	0.0001
Spontaneous pain (%)	83	11.4	100	37.1	0.0012
Walking pain (%)	97	57	100	74.2	0.002
Pain when standing (%)	68.6	34.2	77.1	54.2	0.008
Prolonged standing pain (%)	71.4	25.7	91.4	51.4	0.0003
Means Lequesne index	6.6	2.4	10.3	5.1	0.0001

% = percentage of patients with pain
VAS: Visual Analog Scale

Table 4.
Indirect comparison of WOMAC total score change from baseline. [18]

	Duloxetine	Ibuprofen	Naproxen	Celecoxib	Etoricoxib	Tramadol	Oxycodone	Hydromorphone
Frequentist analysis								
Number of studies	3	2	7[f]	14[f]	5	5	2	2
Change from baseline vs. placebo, mean	−6.48	−8.34	−8.27	−5.78	−11.04	−3.99	−8.56	−2.13
95% CI	[−9.09, −3.88]	[−11.98, −4.71]	[−10.27, −6.28]	[−6.86, −4.69]	[−13.24, −8.84]	[−6.74, −1.23]	[−17.23, 0.11]	[−5.99, 1.72]
I^2 (%)	44.35	0	51.92	32.49	0	58.03	71.99	63.54
Indirect vs. Duloxetine [a]	NA	−1.86	−1.93	0.71	−4.56	2.36	−2.07	4.35
95% CI[b]	NA	[−6.33, 2.62]	[−4.70, 0.84]	[−2.12, 3.53]	[−7.97, −1.15]	[−1.00, 5.73]	[−11.13, 6.98]	[−0.31, 9.01]
Bayesian analysis								
Number of studies contributing to each compound[c]	3	2	9	16	5	5	2	2
Change from baseline vs. placebo, mean[d]	−6.47	−7.85	−7.9	−6.2	−9.53	−2.89	−7.04	−2.19
95% CI	[−9.27, −3.7]	[−11.59, −4.18]	[−9.54, −6.27]	[−7.46, −5.03]	[−11.86, −7.3]	[−5.41, −0.54]	[−11.35, −2.95]	[−5.52, 1.21]
Indirect vs. Duloxetine[a]	NA	−1.38	−1.43	0.27	−3.07	3.57	−0.58	4.28
95% CI[b]	NA	[−6.04, 3.21]	[−4.65, 1.81]	[−2.78, 3.28]	[−6.66, 0.49]	[−0.17, 7.19]	[−5.69, 4.32]	[−0.01, 8.69]
Probability Duloxetine is Superior	*NA*	*0.28*	*0.19*	*0.57*	*0.04*	*0.97*	*0.41*	*0.97*
Number of studies contributing to each compound for adjusted for baseline WOMAC score[e]	3	2	7	14	5	3	1	1
Indirect vs. Duloxetine adjusted for baseline WOMAC score[e]	NA	1.85	0.24	0.83	−0.43	4.92	−4.67	8.19
95% CI[b]	NA	[−2.13, 5.9]	[−2.36, 2.87]	[−1.45, 3.14]	[−3.4, 2.57]	[1.51, 8.34]	[−13.24, 4.07]	[3.84, 12.56]
Probability Duloxetine is Superior	*NA*	*0.82*	*0.57*	*0.76*	*0.38*	*1*	*0.15*	*1*

[a] A positive (negative) result indicates that the compared treatment is worse (better) than duloxetine.
[b] If zero does not fall between the upper and lower bounds the null hypothesis (treatments are the same) is rejected.
[c] There are fewer studies in the adjusted analyses.
[d] Random effects model.
[e] Random effects model adjusting for baseline excluding trials with no baseline.
[f] 2 studies without placebo arms were not included in the frequentist analysis.

Table 5
VAS, Lequesne and WOMAC scores in the Ozone and Control groups at Baseline, at 6 weeks and at 3, 6 and 12 months after treatment.[21]

Time-point/group	VAS	Lequesne	WOMAC			
			Pain	Stiffness	Physical function	Total
Baseline						
Ozone group	7.52±1.57	15.07±3.82	12.36±2.79	2.95±1.75	55.12±6.99	70.43±8.37
Control group	7.66±1.32	14.26±2.64	13.55±3.45	3.32±2.04	57.45±6.16	73.68±10.07
P-value[a]	0.682	0.280	0.091	0.394	0.120	0.119
6 weeks						
Ozone group	3.69±1.14	5.86±2.40	4.90±2.25	1.67±1.12	28.55±5.00	35.12±6.23
Control group	4.53±1.67	7.89±2.71	6.97±2.45	2.42±1.31	33.84±6.26	43.24±7.08
P-value[a]	0.010	0.001	<0.001	0.008	<0.001	<0.001
P-value[b]	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
P-value[c]	<0.001	<0.001	<0.001	0.014	<0.001	<0.001
3 months						
Ozone group	3.81±1.57	6.02±2.05	5.69±2.32	2.00±1.12	28.98±7.35	36.67±8.11
Control group	4.74±1.54	8.97±2.14	7.71±2.04	2.61±1.33	34.82±7.61	45.29±8.51
P-value[a]	0.009	0.046	<0.001	0.034	<0.001	<0.001
P-value[b]	<0.001	<0.001	<0.001	0.002	<0.001	<0.001
P-value[c]	<0.001	<0.001	<0.001	0.049	<0.001	<0.001
6 months						
Ozone group	4.71±1.42	7.19±2.24	5.83±1.81	2.25±1.47	29.95±6.67	38.02±7.66
Control group	5.97±1.23	9.21±2.04	7.95±1.90	2.76±1.56	36.50±8.77	47.00±8.70
P-value[a]	<0.001	0.037	<0.001	0.042	<0.001	<0.001
P-value[b]	<0.001	<0.001	<0.001	0.021	<0.001	<0.001
P-value[c]	<0.001	<0.001	<0.001	0.126	<0.001	<0.001
12 months						
Ozone group	5.17±1.43	8.74±2.89	6.71±2.38	2.33±1.37	32.76±6.64	41.19±7.64
Control group	6.76±1.45	10.08±3.03	8.55±2.44	2.68±1.47	37.87±6.96	58.84±7.48
P-value[a]	<0.001	0.046	<0.001	0.047	0.001	<0.001
P-value[b]	<0.001	<0.001	<0.001	0.032	<0.001	<0.001
P-value[c]	0.008	<0.001	<0.001	0.080	<0.001	<0.001

Table 6.1 Comparison of WOMAC pain scores at 3, 6, and 12-month intervals.[26]

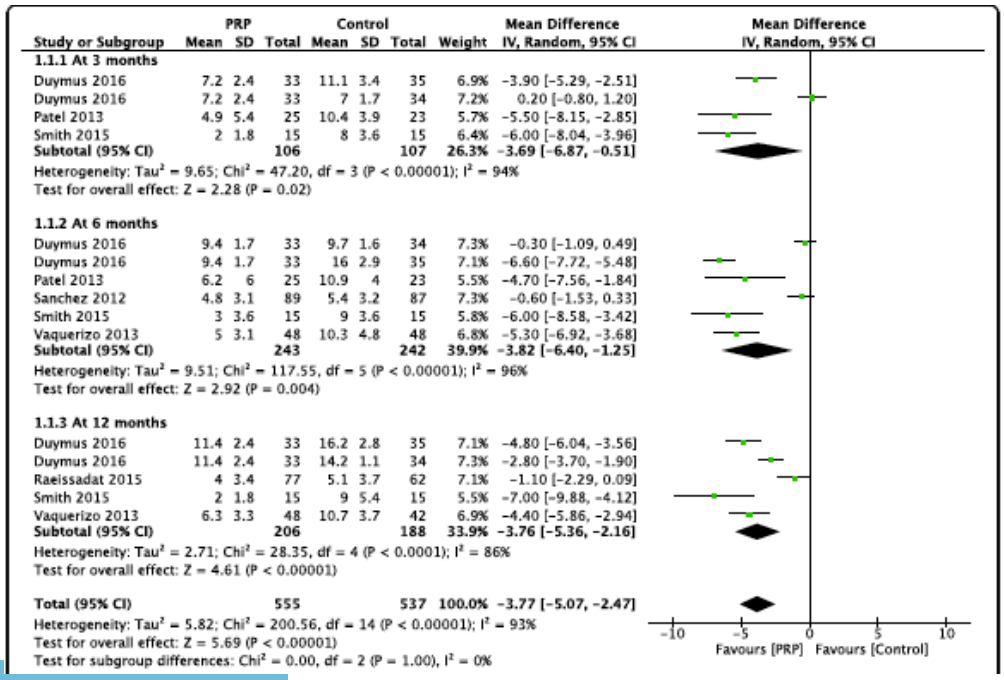


Table 6.2 Comparison of WOMAC physical function scores at 3, 6, and 12-month intervals.[26]

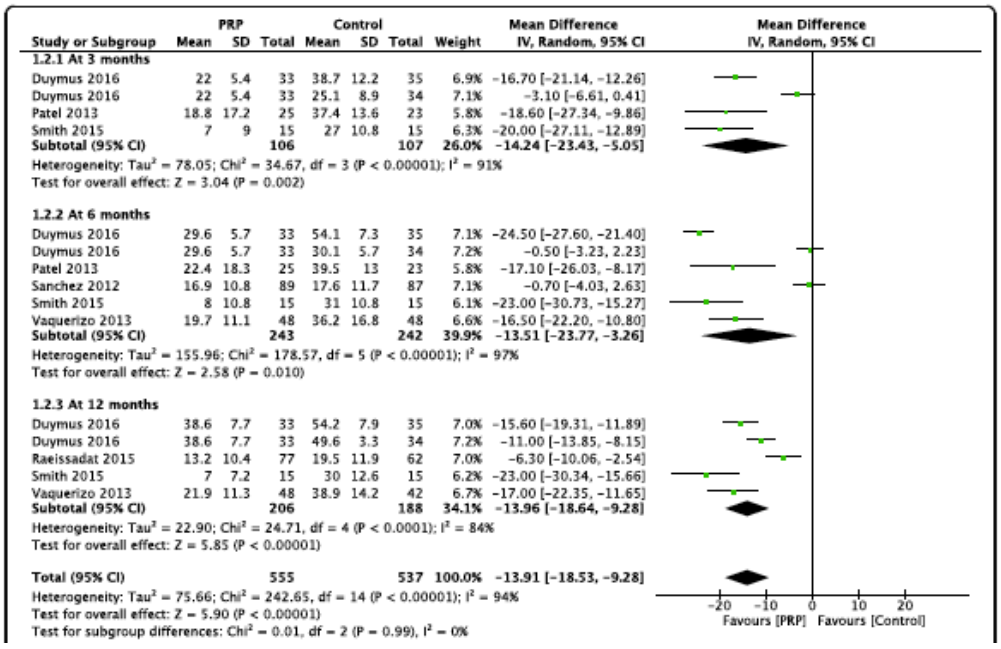


Table 6.3. Comparison of total WOMAC score at 3, 6, and 12-month intervals.[26]

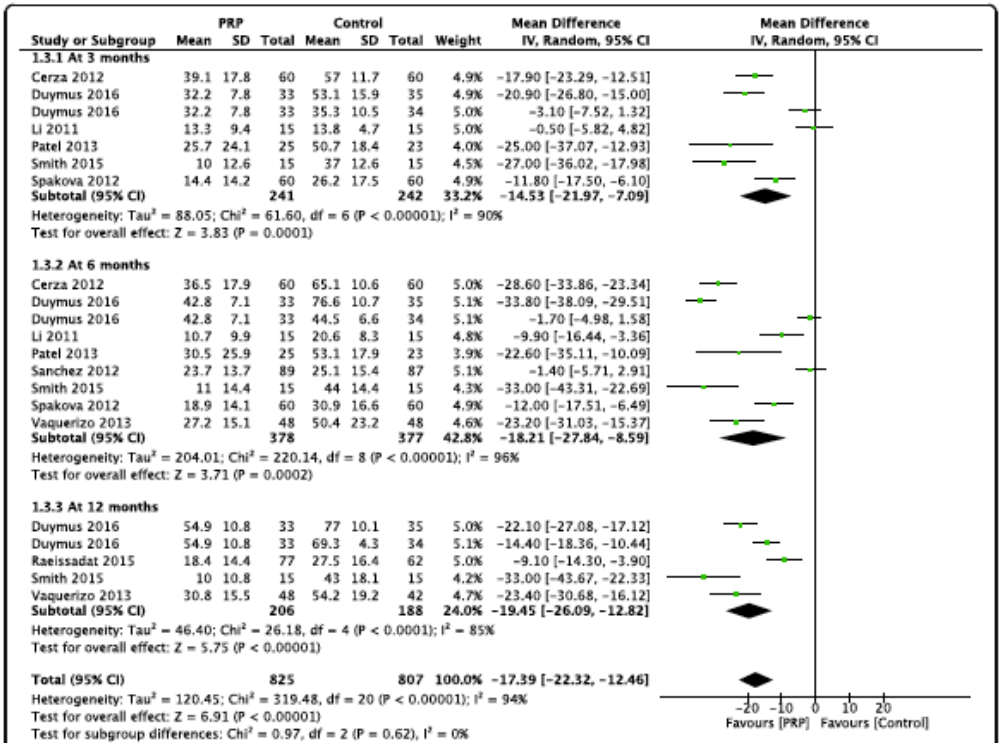


Table 7.1
Comparison of outcomes at 6 months.[27]

	PRP	HA	NSAID	P
Patients	33	32	33	
Responders [no. (%)]				
20% decrease WOMAC pain	16 (48)	7 (21)	5 (15)	< 0.001
20% decrease WOMAC stiffness	15 (45)	5 (15)	4 (12)	< 0.002
20% decrease WOMAC physical function	15 (45)	5 (15)	4 (12)	< 0.05
20% decrease VAS	16 (48)	8 (25)	6 (18)	< 0.021
Change from baseline				
WOMAC pain				
% change from baseline	− 22.38	− 14.5	− 5.9	< 0.001
End of follow-up	4.72 ± 0.87	5.15 ± 0.84	5.75 ± 0.43	< 0.005
WOMAC stiffness				
% change from baseline	− 18.3	− 0.5	2.9	< 0.05
End of follow-up	3.36 ± 0.5	3.56 ± 0.5	4.18 ± 0.39	< 0.001
WOMAC physical function				
% change from baseline	− 21.1	− 12	0.6	< 0.001
End of follow-up	± 0.6	28.62 ± 0.9	32.69 ± 0.8	< 0.001
WOMAC total				
% change from baseline	− 21.06	− 12,39	− 0.06	< 0.03
End of follow-up	33.6 ± 1.2	37.34 ± 1.2	42.63 ± 1.02	< 0.002
VAS				
% change from baseline	− 20.2	− 13.92	− 5.4	< 0.001
End of follow-up	4.9 ± 0.52	5.21 ± 0.6	5.81 ± 0.39	< 0.001

Table 7.2
Comparison of outcomes at 12 months.[27]

	PRP	HA	NSAID	P
Patients	33	32	33	
Responders [no. (%)]				
20% decrease WOMAC pain	10 (30)	0	0	< 0.001
20% decrease WOMAC stiffness	9 (27)	0	0	< 0.001
20% decrease WOMAC physical function	8 (24)	0	0	< 0.05
20% decrease VAS	5 (15)	0	2(6)	< 0.001
Change from baseline				
WOMAC pain				
% change from baseline	− 20.39	− 1.03	− 6.4	< 0.03
End of follow-up	4.84 ± 0.7	5.96 ± 0.4	5.72 ± 0.45	< 0.001
WOMAC stiffness				
% change from baseline	− 16.1	− 0.7	4.9	< 0.001
End of follow-up	3.45 ± 0.5	4.03 ± 0.3	4.27 ± 0.45	< 0.002
WOMAC physical function				
% change from baseline	− 19	0.3	0.9	< 0.001
End of follow-up	26.21 ± 0.8	32.65 ± 0.7	32.78 ± 0.73	< 0.05
WOMAC total				
% change from baseline	− 18.9	0.07	0.2	< 0.001
End of follow-up	34.51 ± 1.2	42.65 ± 0.9	42.78 ± 1.02	< 0.02
VAS				
% change from baseline	− 18.2	3	− 6.4	< 0.001
End of follow-up	5.03 ± 1.7	6.25 ± 0.4	5.75 ± 0.43	< 0.001

Table 8.1
Comparison of functional limitation between the PRP and PRL groups. [33]

					Repeated-measures test	Pairwise comparisons*
	Pretreatment	First month	Second month	Sixth month	All	
PRL	47.3±6.7	31±6.3	25±5.5	27.8±5.2	<0.001	All of *P*-values were ≤0.001 except for comparison between (1 vs 6) that was 0.004
PRP	47.8±4.7	30.3±7.6	19.6±7.2	22.8±7.9	<0.001	All *P*-values were ≤0.001

Table 8.2
Comparison of pain between the PRP and PRL groups [33]

					Repeated-measures test	Pairwise comparisons*
	Pretreatment	First month	Second month	Sixth month	All	
PRL	14.6±1.4	9.5±2.3	7.1±1.7	8±1.6	<0.001	All *P*-values were ≤0.001 except for comparison between (1 vs 6), which was 0.004
PRP	14.8±1.5	9.2±2.7	5.4±1.8	6.2±2.1	<0.001	All *P*-values were <0.001 except for comparison between (1 vs 6), which was 0.015 and comparison between (2 vs 6) that was 0.022

Table 8.3
Comparison of stiffness between the PRP and PRL groups [33]

					Repeated-measures test	Pairwise comparisons*
	Pretreatment	First month	Second month	Sixth month	All	
PRL	5.2±1.3	3.2±1.1	2.6±0.7	3±0.7	<0.001	All *P*-values were <0.001 except for comparison between (1 vs 2), which was 0.018, comparison between (1 vs 6), which was 0.28, and comparison between (2 vs 6), which was 0.14
PRP	5.4±1.2	3.3±1.1	2.1±0.7	2.5±0.8	<0.001	All of *P*-values were ≤0.001 except for comparison between (2 vs 6), which was 0.071

Table 8.4
Comparison of WOMAC scores between the PRP and PRL groups [33]

					Repeated-measures test	Pairwise comparisons*
	Pretreatment	First month	Second month	Sixth month	All	
PRL	67.1±7.9	43.8±8.2	34.8±6.9	38.7±6.6	<0.001	All *P*-values were <0.001 except for the comparison between (2 vs 6), which was 0.003
PRP	67.9±7.3	42.9±10.85	27.1±9.1	31.4±10.2	<0.001	All *P*-values were <0.001 except for the comparison between (1 vs 6), which was 0.002

Table 9
Outcomes measure for Kovar et al. at baseline and after intervention.[42]

Measure	Baseline		Post-Intervention		*P* Value†
	Intervention Group (n = 47)	Control Group (n = 45)	Intervention Group (n = 47)	Control Group (n = 45)	
6-minute walk, *m*	381 ± 114	356 ± 130	451 ± 118	339 ± 125	< 0.001
AIMS subscales					
Physical activity	6.15 ± 2.27	5.72 ± 2.49	3.74 ± 2.69	5.96 ± 2.32	< 0.001
Arthritis impact	4.56 ± 2.14	3.85 ± 2.38	2.86 ± 1.88	3.06 ± 1.91	0.093
Arthritis pain	5.15 ± 1.99	4.87 ± 2.31	3.77 ± 1.73	4.77 ± 2.12	0.003
Medications use	2.80 ± 1.65	2.64 ± 1.68	3.64 ± 1.92	2.90 ± 2.02	0.08

Appendix B

Figures

Figure 1

Joint space narrowing in patients completing each year of the study. [16]

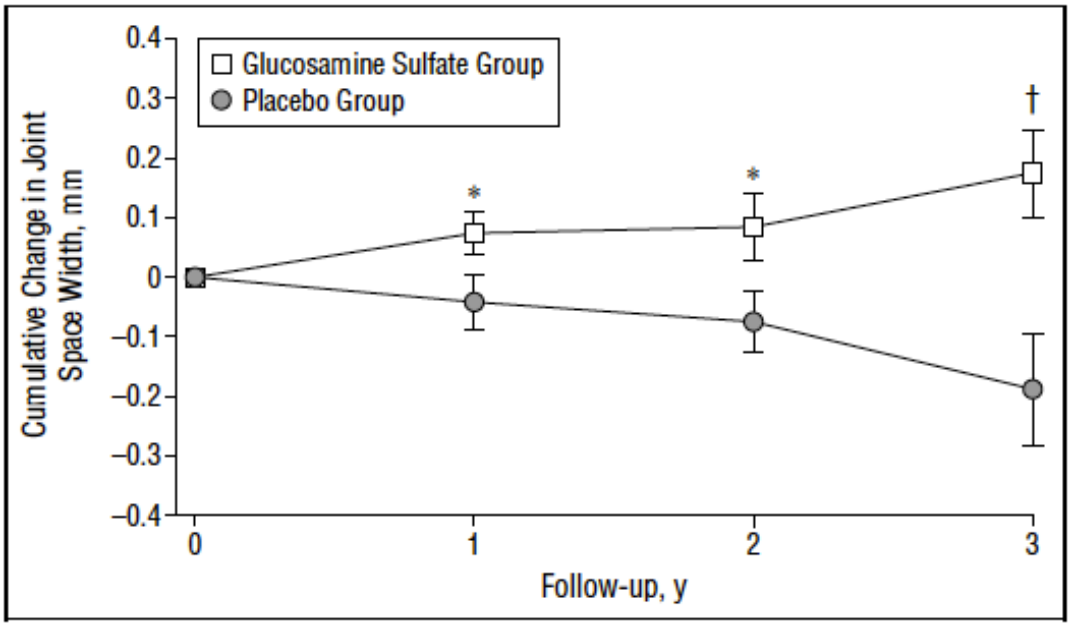


Figure 2

Visit-wise change from baseline mean BPI average pain severity score in all subgroups.[17]

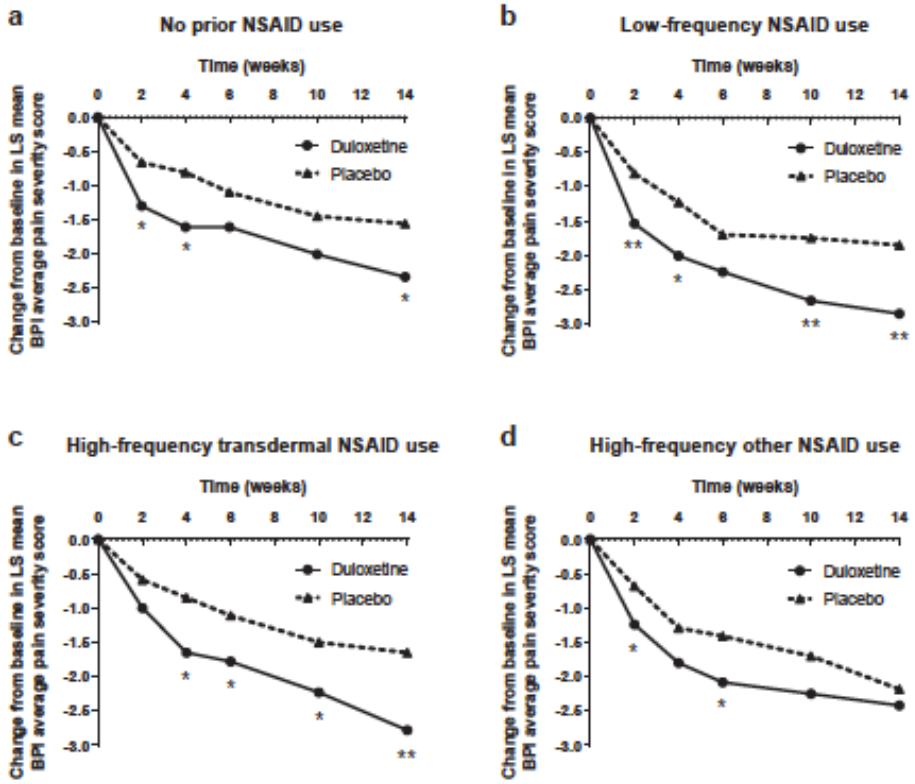
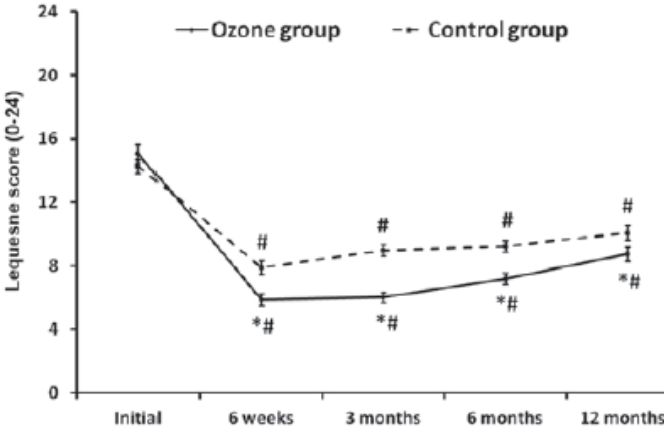
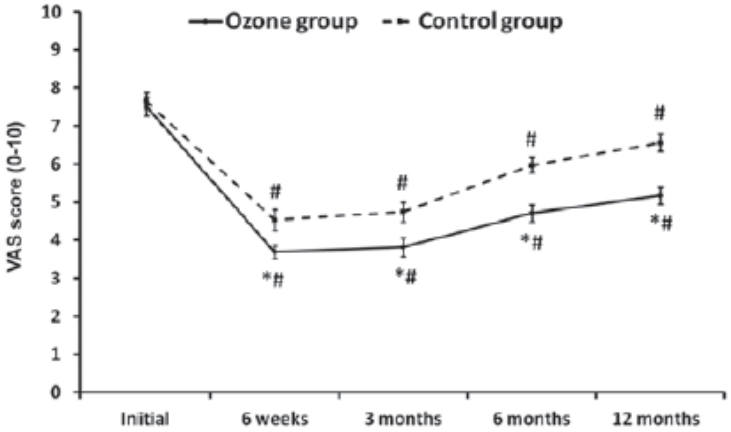


Figure 3.1



Lequesne scores in the groups pre- and post-treatment. P<0.05 vs control group; P<0.05 vs. baseline

Figure 3.2



VAS scores in the groups pre- and post-treatment. P<0.05 vs. control group; P<0.05 vs. baseline. VAS, Visual Analogue Scale

Figure 4.1

Comparison of Lesquesne and WOMAC general scores in the hyaluronic acid group versus MSC.[32]

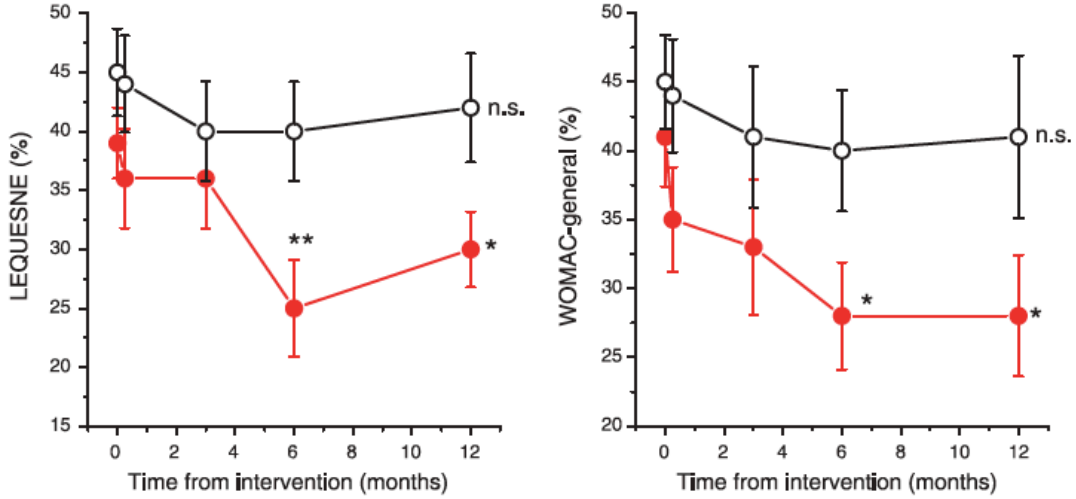


Figure 4.2

Comparison of VAS and WOMAC pain sub-scores in hyaluronic acid versus MSC.[32]

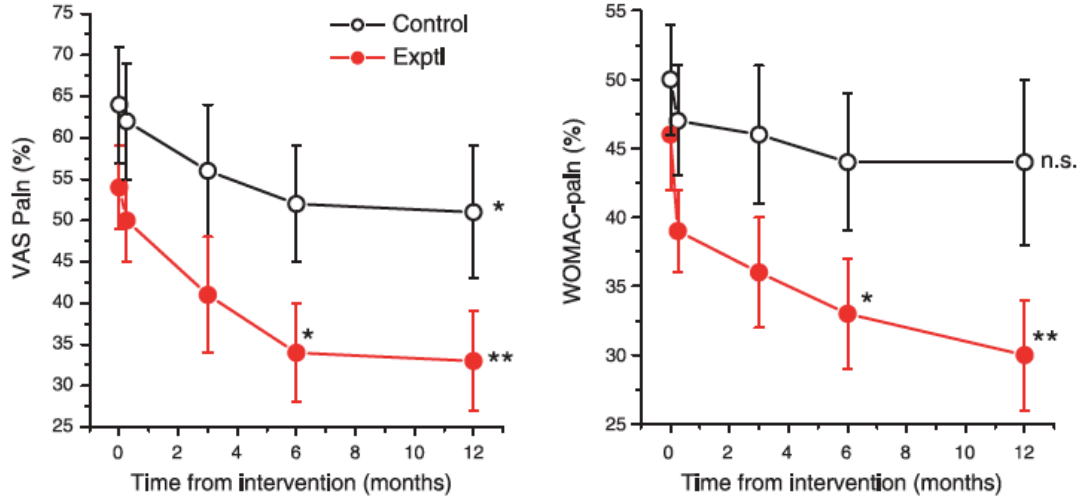
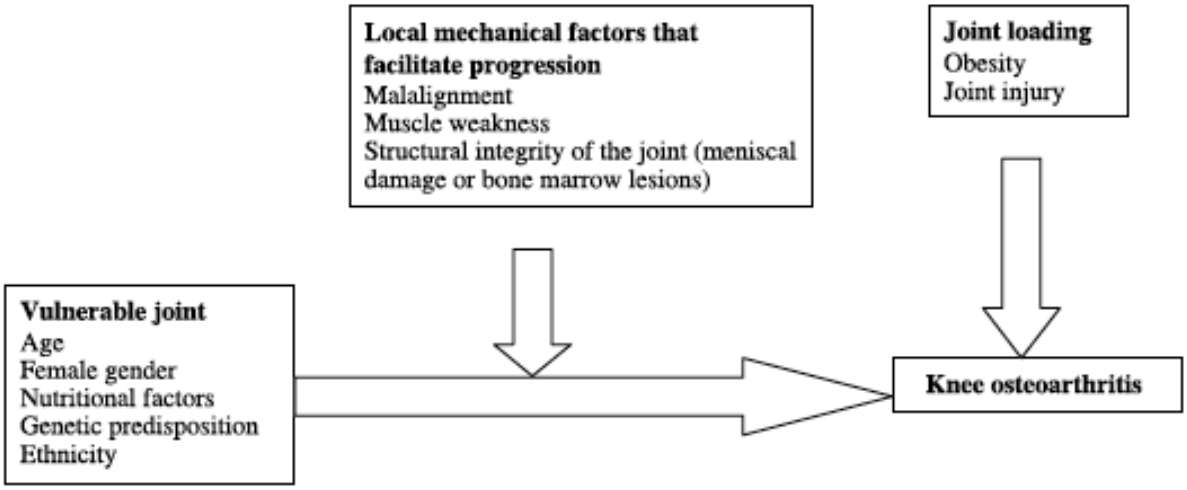


Figure 5
Risk factors for development or progression of knee osteoarthritis.[40]



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