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Stem Cell Therapy as an Alternative for Osteoarthritis of the Knee

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STEM CELL THERAPY AS AN ALTERNATIVE FOR OSTEOARTHRITIS OF THE KNEE

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Introduction

Imagine this: you wake up one morning, and it hits you. Today is going to be far worse than yesterday. The sound of bone on bone grinding is not just in your head anymore. You can hear your knee crack and cry out as you struggle to get out of bed. Once you manage to thrust yourself to a standing position, you become dizzy. Bam! Now you've hit the ground. You just hope that you haven't broken another bone. Your family hears you fall and comes running. You fake a smile and say that you're okay. Deep down you know you're not though. You can barely move. Your knee is swollen, and you have no muscle mass. You look at yourself in the mirror ashamed. You were the captain of the hockey team and always had dreams of becoming a professional. You used to love going to work and going to the gym with your friends. Now all you can do is sit at home. You barely recognize that person staring back at you in the mirror. You are not in shape. You have put on a lot of weight. Most importantly, you are miserable, and you are told there is nothing you can do except take medications and wait. You are too young for a total knee replacement. You start to feel hopeless.

This hopelessness is the everyday feeling of Julia*[1]. In high school, Julia tore her meniscus during a hockey game. She received a surgery in which the entire meniscus was removed in order to repair it. The job of the meniscus is to protect the articular cartilage of the knee. Because of her exposed cartilage, Julia had an increased risk of developing osteoarthritis after this injury, but her love of hockey was too great to give up. She continued to push her knee, so that she could play hockey at a Division 1 college. She now cannot exercise. She can barely walk without excruciating pain. Julia wants to fix her condition, but she doesn't know how. She is worried about potential side effects caused by taking medications for too long.

[1] *Individuals referenced are not real patients

Henry* lives nearby and also struggles with osteoarthritis. His struggle is different though. Henry is 66 years old and has always been a bigger man. He started experiencing knee pain about 20 years ago. His parents both had two knee replacements, so he assumed knee pain just came with age. His friends told him to try to lose weight, but Henry always complained. Henry knew exercising made his knees hurt more. To try to ease his pain, Henry started taking anti-inflammatory medications 15 years ago. He hoped that he could continue to stay on these medications for longer, but that has not been the case. Henry had an ulcer potentially caused by the medications last year. Since, he has started to notice the medication does not seem to be working as well. Henry now has a very difficult time getting up out of chairs to stand because of the pain. His knee is noticeably swollen and always feels warm in the joint. Henry's knee has begun to creak when he walks which has become embarrassing for him. His doctor also informs him that with his current weight, he is at an increased risk for cardiovascular complications. Henry and his doctor have begun to discuss a total knee replacement in his near future.

Though both Julia and Henry have osteoarthritis, they have different needs. The two of them are told about an experimental procedure that could potentially improve their quality of life. It is a new therapy using injections of stem cells which are cells that can differentiate into any bodily tissue. It has not been approved for large scale usage yet, but a hospital nearby is accepting individuals willing to try it. Should Henry and Julia try it?

The purpose of this project was to investigate the possibility of stem cell therapy becoming a prominent treatment for osteoarthritis as an alternative to the use of anti-inflammatory medications before a total knee replacement. Stem cell therapy is a rapidly growing technique for treating diseases. For about 30 years, stem cell therapy has been used to treat blood and bone marrow disorders, leukemia, and immune disorders (University of Utah,

2014). In particular, I think that stem cell therapy would be most useful for those individuals such as Julia who are too young for a total knee replacement but cannot continue to live with the pain of osteoarthritis. These individuals often fall into what is known as the treatment gap. The treatment gap exists because there is no known treatment for these younger individuals who still struggle every day with osteoarthritis. Treatment for osteoarthritis needs to be individualized, and I was interested in discovering whether stem cell therapy would be beneficial for both, one, or neither Julia and Henry. I have researched the treatment, the cost, the side effects, and the potential benefits of using stem cell therapy. Stem cell therapy for osteoarthritis could transform the lives of individuals such as Julia and Henry by relieving their suffering and giving them a second chance at a relatively risk-free active lifestyle. Stem cell therapy could lower costs and limit the number of surgeons and physical therapists needed to care for osteoarthritis patients alone.

In this thesis, I introduce the disease of osteoarthritis and the popular treatments in use for patients today. I will pay specific attention to the knee replacement because it is the most common treatment for end stage osteoarthritis. Finally, I will look at the up and coming stem cell therapy for osteoarthritis of the knee through an examination of case studies currently being run around the world. To conclude, I will suggest which treatment appears to be the best treatment for each specific patient.

Osteoarthritis

In our society, the elderly and obese populations are increasing steadily. These populations are the most at risk for osteoarthritis. Osteoarthritis is now the most common form of joint disease worldwide. In the United States, about 12 percent of the population struggle each day with pain caused from osteoarthritis (Zhang et al, 2010). It is estimated that 1 in 10 Canadians over the age of 15 struggle with osteoarthritis (Khan, et al, 2018). Osteoarthritis is often referred to as a "wear and tear" disease though some forms can be caused by genetics. Phrases such as these implicate that there is no modification that can be done to cure osteoarthritis. Osteoarthritis remains the most common reason for patients to undergo total joint replacements (Khan et al, 2018).

The cause of osteoarthritis remained a mystery for a long time until the discovery of degrading enzymes in cartilage in the 1980s (Vincent et al, 2018). Degrading enzymes can be enhanced by damage to cartilage caused by a destabilizing injury that leaves an upregulation of matrix metallopeptidase (MMP), an enzyme involved in normal cartilage turnover. Osteoarthritis is characterized by a loss of articular cartilage which covers the end of bones (Figure 1). The loss of cartilage occurs originally at the articulating surface or adjoining surface of the joint then spreads through the bony matrix or surface of the bone until it reaches the subchondral bone or the layer of bone directly below the cartilage. Cartilage is made up of cells called chondrocytes. These cells are responsible for maintaining the bony matrix, but they are also the cells which synthesize degrading enzymes in cartilage. Changes in the tissue caused by loss of cartilage include patchy loss of aggrecan which is a protein that is responsible for the load-bearing property of cartilage, clustering of chondrocytes, and bony expansion of the joint with osteophyte or bony spur formation due to increased stress on the joint. Severe joint pain results

because as articular cartilage is damaged, it produces factors such as nerve growth factor. Nerve growth factor sensitizes local pain fibers which leads to chronic pain (Vincent et al, 2018).

Several key symptoms determine diagnosis of osteoarthritis. Osteoarthritis includes severe joint pain and functional limitation of the joint. The development of symptoms can be acute and can affect one or more joints. Joint pain can either involve pain only during weight bearing periods or it can be persistent. Osteoarthritis causes the affected joints to be swollen. Muscle wasting and joint deformity as well as restricted range of motion and joint crepitus or bone cracking are often noted in individuals with osteoarthritis. X-rays are often used to determine the severity of osteoarthritis. X-rays show the presence of osteophytes around the joint. The Kellgren-Lawrence scale is used to diagnose osteoarthritis in X-rays (Figure 2). A rating of 0 is a normal joint whereas a rating of 4 shows severe joint gap narrowing indicating the end stage of the disease (Vincent et al, 2018).

Unfortunately, there are several external factors which can put people at risk for osteoarthritis. The first risk factor is mechanical load. Mechanical load is defined as the total load placed on a joint. There are two circumstances of abnormal load which can cause damage. The first is placing abnormal load on an undamaged joint. This is the case of an obese individual. In addition, adipocytes, which are cells that make up fat tissue, are known to secrete inflammatory cytokines or immune signaling molecules that can cause cartilage matrix degradation (Vincent et al, 2018). The second is placing normal load on a joint that has lost its protective mechanisms for joint movement. Either of these circumstances cause abnormal stress and damage to the joint which can result in the development of osteoarthritis. It has been found that young athletes who sustained knee joint injuries such as anterior cruciate ligament (ACL) tears have an increased risk of osteoarthritis (Vincent et al, 2018). Individuals who work in

occupations in which their joints are repetitively damaged in low impact injuries are also often at higher risk for osteoarthritis (Khan et al, 2018). Both of these injuries cause the joint to experience abnormal load because the protective mechanisms of joint motion such as the ligaments have been damaged.

Two additional risk factors are age and genetics. On average, individuals over the age of 50 develop symptoms of osteoarthritis (Anderson et al, 2010). Aged joints are more likely to experience mechanical failure due to loss of muscle strength which can cause an abnormal gait. Cartilage matrix synthesis is reduced while degradative pathways are increased as an individual ages (Vincent et al, 2018). The combination of these two events leaves older cartilage prone to degradation. As for genetics, twin studies have found that heritability in osteoarthritis is about 60% meaning that genes play a large role in determining if an individual will have osteoarthritis. (Vincent et al, 2018). It has been found that osteoarthritis is polygenic (Chapman et al, 2012). This means that the disease is increased by changes in several different genes, so the risk of each individual gene is relatively small.

Treatment Options

Treatment for osteoarthritis depends on the severity of the disease as well as on the individual being treated. Treatments are divided into three main categories- noninvasive treatments, injectable therapies, and surgical treatments. The noninvasive treatments are the first treatments used for individuals trying to manage the onset of osteoarthritis. The first noninvasive treatment is weight loss. Studies have shown that every kilogram of weight loss correlates to a quadruple decrease in forces across the knee (Khan et al, 2018). It is recommended that individuals do low-impact aerobic exercise such as swimming to promote weight loss as well as

cardiovascular health while also limiting damage to injured joints. Knee bracing is another less well known noninvasive treatment option. Knee bracing is not often used due to the limited quantity of evidence showing that it is beneficial. Physical therapy is another noninvasive treatment which can help to strengthen the quadriceps muscles. Strengthened quadriceps reduce load and direct force applied to the knee during movement so that stress is minimized (Fransen et al, 2015). The use of oral or topical anti-inflammatory medications (NSAIDs) is the last and most popular noninvasive treatment. It has been found that 65% of osteoarthritis patients in the United States are prescribed a nonsteroidal anti-inflammatory medication with diclofenac (150 mg/day) being the most effective (da Costa et al, 2017). Oral medications have the fourfold risk increase of upper gastrointestinal bleeding. Topical nonsteroidal anti-inflammatory drugs are becoming more common for treatment of osteoarthritis. The most popular topical drugs are diclofenac and ketoprofen (Sardana et al, 2017). These drugs work by reducing hormones that cause pain and inflammation in the body. Both drugs, however, have side effects of dizziness, vomiting, increased blood pressure, swelling in arms or legs, and in more severe cases, ulcers and gastrointestinal bleeding (da Costa et el, 2017).

Injectable therapies and surgical therapies are used only if noninvasive treatments prove fruitless. There are three types of injectable therapies. The first injectable therapy is viscosupplementation which injects a thick liquid into the knee joint space between the cartilage (Figure 1). Viscosupplementation adds viscoelasticity and shock absorption to synovial fluid, located in the knee joint space, which helps to maintain smooth joint movement and contains both anti-inflammatory and chondroprotective properties (Bellamy et al, 2006). There are several different formulas and dosing techniques so that each treatment program can be chosen for the individual being treated. The second type of injectable therapy is corticosteroids which are anti-

inflammatory drugs. It has been found that these injections result in short-term pain improvement, but the effects decrease with long-term use (Khan et al, 2018). The last type of injectable therapy is known as combination therapy. Combination therapy is the simultaneous injection of more than one of the above injectable therapies to improve osteoarthritic pain (Khan et al, 2018).

Surgical therapies are the last "option" for individuals struggling with osteoarthritis. Many individuals with end stage osteoarthritis opt for surgery because the pain is too much to live with. The first type of surgery is known as tibial osteotomy. A tibial osteotomy reshapes the tibia to realign the knee. The procedure is used to either delay or to avoid a total knee replacement. It also allows the individual to remain active by preserving joint mechanics (Niinimaki et al, 2012). A study done between 1987 and 2008 found joint survivorship of 89% at 5 years and 73% at 10 years after individuals had a tibial osteotomy (Niinimaki et al, 2012).

The second surgical treatment is a unicompartmental knee arthroplasty also known as a partial knee replacement. This surgery can only be performed for cases of monocompartmental osteoarthritis where only one joint surface is damaged. Candidates for this surgery are at significant risk for revision surgery if they are younger than 55 years old due to higher demands on knee function and longer life expectancy (W-Dahl et al, 2010). It is easier to return to an active lifestyle after a partial knee replacement as opposed to a total knee replacement. The percent of return to sport after this surgery was 75% to greater than 100%, meaning that more individuals lived active lifestyles after surgery than before (W-Dahl et al, 2010).

The final surgical option is a total knee replacement which is only done after all other options have been exhausted due to the surgery's high cost, potential for revision surgery or infection, and minimal increase in quality of life. Total knee replacement is effective in

improving function and limiting pain. The implant survival depends on the individual's activity level, bone quality and age, and fixation method of the implant (Losina et al, 2012). Total knee replacements are not recommended for patients younger than 60, however. Knee replacements tend to only last about 20 years, so younger patients would potentially need revision surgery later in life. Because total knee replacements are the most popular surgical option today, they are being compared to the new stem cell therapy. To accomplish this, knee replacements will be dissected further.

Knee Replacements

Background

There are more than 600,000 total knee replacements done every year in the United States (Ortho Info). The average patient is normally between the age of 50-80, and there is no weight limit. The demand for total knee replacements is projected to increase 601% by the year 2030 due to increasing obesity rates and baby boomers headed into retirement (Turner 2011). Total knee replacements become the only option after pain medications and supportive walking devices such as bracing no longer aid the individual enough to keep them moving.

The price of a knee replacement in the United States is averaged at $49,500 (BWH, 2019). This includes the number of days in the hospital, the length of time spent in the operating room, and the type of implant. Inpatient charges are charges acquired while an individual is in the hospital. Inpatient charges typically add about $7,500. There are also outpatient costs when the individual is not in the hospital such as extended physical therapy and follow-up appointments. Depending on the insurance coverage, the average individual is often paying hundreds to thousands of dollars out of pocket. There are also additional costs to ensure that the individual's house is accessible for the person. The individual may not be able to work for several weeks, so it is important to note that loss in salary if the individual does not qualify for disability insurance (BWH, 2019). One option to save money is to consider having the surgery performed in another country, but it is important to make sure the surgeon is accredited by the Joint Commission International.

Procedure

Before receiving a total knee replacement, an orthopedic examination must be performed by the surgeon. The surgeon will assess the individual's medical history, knee function, x-rays, and any other tests needed such as an MRI. The individual should also prep for post-surgery. They will be unable to take care of themselves for a little while, so each patient will need someone to care for them until they can walk with crutches. Some household modifications might need to be made. These include adding safely rails and seats to the stairways and showers (AAOS, 2019). One might also consider living on the lowest level of their home.

Depending on the individual's past medical history, anesthesia is chosen. Either general anesthesia or local anesthesia from the waist down is chosen. During a total knee replacement, the joint is resurfaced. The areas of cartilage which were damaged are removed from the knee joint along with a thin layer of bone. The removed areas are replaced with metal devices. A plastic spacer is placed between the metal components to reduce friction for a smooth gliding surface (AAOS, 2019). In some cases, the patella is also resurfaced and replaced with a metal button. The whole procedure takes about one to two hours. The procedure is done with the patient lying in a supine position with their knees flexed. A 6-inch cut is made down the midline of the knee joint before moving the tendons and muscles aside to access the joint (Turner, 2011).

There are serious complications in less than 2% of the people who receive knee replacements (AAOS, 2019). These complications can include infections of the wound area, blood clots in the leg vein, implant problems, increased pain, and neurovascular injury.

Care

After the surgery, the individual remains in the hospital for a few days. The pain is managed using either opioids or non-steroidal anti-inflammatory drugs (NSAIDs). The individual must also do some blood clot prevention such as moving their ankle and foot or wearing compression stockings. Physical therapy also begins the day after surgery. The first step is often a continuous passive motion machine which helps to move the leg and evaluate it, which prevents stiffness (BWH, 2019). By the time one is discharged from the hospital, they must be able to walk 25 feet as well as climb and descend stairs, get in and out of bed using a cane, and bend their knee to 90 degrees (BWH, 2019). The physical therapy process after a total knee replacement is an extensive one. The ultimate goals by the sixth week after surgery include decreased swelling and increased range of motion, walking about half a mile, and being able to resume everyday activities and chores. The next check point is week eleven. By this point, the individual typically can resume driving and other recreational activities such as walking long distances or swimming. Some sample physical therapy exercises at this point include knee bends, single-leg balancing, and hip abductions (BWH, 2019). Full recovery from a total replacement can take up to one year. To be considered fully recovered one must be pain free and have 115 degrees of movement in their knee.

Outcomes

More than 90% of people who receive a knee replacement experience significant reduction in pain and increased ability to perform activities of daily living (AAOS, 2019). It is important to know that there should be no high intensity exercises after a knee replacement. The individual should not run, jog, or jump because it will increase the rate of deterioration of the plastic spacer causing the knee to become painful again. The knee that received the replacement

will not likely gain full range of motion (Turner 2011). The new knee is also prone to a clicking sound or feeling after surgery which should diminish after time. Currently, about 90% of all knee replacements last at least 15 years with proper care. On the other side, one third of those who receive a knee replacement continue to live in some pain (AAOS, 2019). This is especially true for younger people who have received knee replacements.

If the arthritis is not extreme enough, the knee replacement should not be done because it does not increase the individual's quality of life. Today, more knee replacements are being done than are properly prescribed. Younger individuals can outlive their knee replacement. The replacement is extremely painful when it wears out and a second surgery is much riskier as bones can break while removing the original metal device. Other methods of treatment such as stem cell therapy are being evaluated for younger people with less extreme symptoms of osteoarthritis.

Stem Cell Therapy

There are several types of stem cells in the human body. All stem cells can divide to form more stem cells and also can differentiate to form other types of tissues (ISSCR, 2019). The types of stem cells differ in where they are located and when in life they appear. The most well-known type of stem cell is the embryonic stem cell. Embryonic stem cells are found inside of the blastocyst which is a ball of cells formed 4 days after conception (ISSCR, 2019). Embryonic stem cells are pluripotent meaning they can become any type of tissue in the body which makes them very useful for medicine and research. There are ethical problems with using embryonic stem cells as an unborn fetus must be used for research. This creates divisions among people due to conflicting consciences of when a fetus becomes a child. Induced pluripotent stem cells are a lab created stem cell. These cells are created in a lab by converting somatic or body cells into a cell that behaves like an embryonic stem cell (ISSCR, 2019). These cells are not exactly like embryonic stem cells, but they are very useful for testing new drugs for treatments without causing any ethical battles. Tissue-specific stem cells are another stem cell found in the body. These cells are like differentiated embryonic stem cells because they are more specialized. These cells can only become cells for the specific tissue in which they live, so they are for replacing damaged cells in these regions (ISSCR, 2019). The last type of stem cell is the mesenchymal stem cell (MSC). These cells come from the stroma which is connective tissue surrounding other tissues. MSCs from bone marrow can make bone, cartilage, and fat cells, but scientists are not certain if these cells are truly stem cells because they are multipotent meaning they cannot form every type of tissue in the body (ISSCR, 2019).

Recently, stem cells were speculated to be potentially effective in treating osteoarthritis. Stem cells used for these procedures would be harvested from individuals' bone marrow or

adipose tissue. Specific stem cells called mesenchymal stem cells or medicinal signaling cells are thought to be able to treat osteoarthritis. Mesenchymal stem cells can sense their environment and secrete large quantities of signaling molecules as a response (Lopa et al, 2018). The actual process of how mesenchymal stem cells repair joint issue is unknown. Recently, studies have found that mesenchymal stem cell derived extracellular vesicles (EVs) protect cartilage against osteoarthritis and promote cartilage repair (De Bari et al, 2018). EVs are membrane enclosed particles which are released from mesenchymal stem cells. They contain biologically active signaling molecules. These cells can bind to target cells to activate intracellular signaling from the plasma membrane for cartilage repair (De Bari et al, 2018). Mesenchymal stem cells are fibroblast-like cells which can form colonies from a single cell. They can also form several different skeletal tissues (van der Kraan, 2013).

There are different types of mesenchymal stem cells that can be harvested from the body and have been used for various clinical trials. Mesenchymal stem cells are in bone marrow and adipose tissue. These MSCs from different locations are theorized to be the same type of cells, but further research might prove otherwise. The first type is bone marrow derived mesenchymal stem cells. In one case study, a 47-year-old woman with severe osteoarthritis received treatment using bone marrow derived mesenchymal stem cells. The woman received 3.6×10^7 cells in a transplant to her knee joint. After 6 months, the MRI revealed that the cartilage covering the distal condyle of the femur and proximal part of the tibia had increased. The woman also experienced less pain, more function of the knee, and increased walking distance without any negative effects (Mehrabani et al, 2016).

The second type of MSC is bone marrow aspirate concentrate which is made from fluid taken from bone marrow. Recent studies have found significant pain reduction and

improvements in function of the knee joint after 12 months of injection with bone marrow aspirate concentrate (Lopa et al, 2018). The third type is stromal vascular fraction from adipose tissue. Stromal vascular fraction includes MSCs along with fibroblasts and white blood cells.

Clinical Trials

A trial done by researchers at Monash University, registered both in Australia and New Zealand, looked at whether the number of injections of stem cell therapies for treating osteoarthritis affected the results seen in patients (Freitag et al, 2019). There were 30 participants with grade two or three osteoarthritis for which conservative treatment of anti-inflammatory medication was ineffective. The participants were either placed in a control group with no injection, received one injection, or received two injections (Freitag et al, 2019). The stem cells were taken from adipose tissue of the abdominal area. The cells were cultured and harvested to make a cell pellet. The cell pellet was suspended in saline to make the injection. Local anesthetic was injected above the joint capsule before the injection. The injection was put into the intra-articular knee space using ultrasound for placement guidance (Freitag et al, 2019). Participants were told to use crutches for four weeks and given quadricep activation exercises. Pain was measured using the Numeric Pain Rating Scale, the Knee Injury and Osteoarthritis Outcome Score, and the Western Ontario and McMaster Universities Osteoarthritis Index. The Numeric Pain Rating Scale asks patients to rate their average pain from 0-10. The Knee Injury and Osteoarthritis Outcome Score measures quality of life and focuses on pain improvement, symptoms, activities of daily living, and use of sport for recreation. The Western Ontario and McMaster Universities Arthritis Index (WOMAC) assesses pain, stiffness, and physical function of the knee. It was found that pain significantly decreased in both injection groups compared to

the control group (Freitag et al, 2019). Quality of life also increased in both injection groups (Figure 3).

After MRI investigation, the two-injection group was the only group to have less cartilage loss and no osteocyte formation (Freitage et al, 2019). The control group and one injection group saw about 50% of participants experiencing osteocyte formation. Many of the participants experienced swelling after their injection, with two participants having swelling for four weeks. The researchers concluded that two injections six months apart were better than the singular injection due to the disease stabilization with two injections (Freitage et al, 2019). This means that the osteoarthritis did not progress with two injections, but it also did not heal completely. These results suggest that stem cells are more supportive such as reducing swelling rather than directly becoming chondrocytes. One strength of this study was that it showed that multiple injections of adipose derived stem cells are safe and effective for treating osteoarthritis. The study did have a weakness, though, being that none of the participants were blinded to their group. There could have been a placebo effect working against the conclusion of the questionnaires. The placebo effect is shown because the control group initially increased their WOMAC score even though they were not injected. The MRI analysis did help to correct some placebo effect because it had to either show disease progression or not compared to baseline MRI.

A recent study was done under the Japanese Act on the Safety of Regenerative Medicine in which 13 participants with either Grade III or IV osteoarthritis received stromal vascular fraction therapy for their knee osteoarthritis (Yokota et al, 2017). The cells were harvested using liposuction of the lower abdomen. Each knee was injected with 3×10^7 stromal vascular fraction cells. The patients did restricted physical therapy in which they aimed to perform 100 “bend and

stretch" exercises the day of the injection and the day after the injection. The patients received oral pain relief medication for three days. The outcomes of the patients were accessed using the VAS for pain, the Japanese Knee Osteoarthritis Measure, and the Western Ontario and McMaster Universities Osteoarthritis Index. All of the patients had improved by about 30% over baseline measurements 1 month after the procedure which were sustained at the 6-month reevaluation (Yokota et al, 2017). There were no serious side effects for any participant during the procedure. There was some pain and swelling around the injection site for a few days. One important strength of this study is that the it is the only case study that is approved under a national act. The Japanese Act on the Safety of Regenerative Medicine was passed in November 2014 to set standards for the use of stem cells in medical clinics (Yokota el al, 2017). These standardization laws for cell culture and processing are important for the use of stem cells because it is difficult to ensure each patient receives the exact same treatment because each person's cells are different.

In the first Canadian mesenchymal stem cell clinical trial, the question of MSC dosage was investigated in twelve participants with severe osteoarthritis of the knee for whom conservative nonsurgical treatments such as anti-inflammatory medications had been ineffective (Chahal et al, 2019). The stem cells used came from bone marrow concentrate in the superior iliac spine. The superior iliac spine contains the most bone marrow in an adult body. To create the stem cell injection, the bone marrow was centrifuged to separate the stem cells (Chahal et al, 2019). Next, the stem cells were cultured for about 30 days. The stem cells were harvested to make the injection. The other cells were analyzed for different types of proteins to see if all stem cells would be similar in each participant. The results used both the Knee Injury and Osteoarthritis Outcome Score and the Western Ontario and McMaster Universities Osteoarthritis

Index to access joint function and quality of life. MRI images were used to evaluate the cartilage before the injection and both 6 and 12 months after the injection. Four patients had local adverse effects after the injection of swelling around the site.

There was a decrease in pain and symptoms as well as an increase in quality of life seen in the patients of all three doses, but the patients in the highest dosage saw the most consistent changes (Figure 4). There were no morphological changes in cartilage 12 months after stem cell injection. This could be because the study chose to include severe osteoarthritis (Stage IV) whereas other studies which saw cartilage changes did not. Cartilage cationic biomarkers which indicate disease progression decreased in the two higher doses. Synovial fluid showed a significant increase in anti-inflammatory and angiogenic biomarkers showing some change taking place in the site (Chahal et al, 2019). These results suggest that the larger dose of 50 million stem cells might be more beneficial than the smaller doses of 1 million or 10 million cells. One strength of these results could be that the biomarkers of osteoarthritis such as increased macrophages decreased with the larger dose of stem cells. This indicates a potential mechanism by which stem cells reduce symptoms of osteoarthritis. Stem cells might reduce the number of macrophages by transforming them into inflammation resolving cells instead (Chahal et al, 2019). The impact of this study is weakened by its relatively small sample size that only included those with advanced osteoarthritis.

A new clinical study is starting in the United States at Emory University. This clinical trial compares injections of corticosteroids with different types of stem cell therapies. The three types of stem cell therapies are bone marrow concentrate stem cells, adipose tissue stem cells, and umbilical cord stem cells (Boden, 2019). In the study, each participant will randomly be given either a corticosteroid injection or a single type of stem cell therapy injection. The study is

recruiting participants between 40 and 70 who have osteoarthritis in one knee that is between Grades II and IV (Figure 2) (Boden, 2019). All subjects will have stem cells taken for both bone marrow concentrate and adipose tissue stem cells to ensure that the study is blinded. The participant will then rate their pain level, their osteoarthritis outcome score, their quality of life, and mental health domains at interval points throughout a year (Boden, 2019). Pain will be measured using the Visual Analog Pain Scale which asks the participant to draw a perpendicular line at the location that best describes their pain intensity and the Knee Injury and Osteoarthritis Outcome Score. Quality of Life will be measured by the EuroQuality of Life which has participants rate their experience with mobility, self-care, usual activities, pain, and anxiety. Mental health will be assessed by the Patient-Reported Outcomes Measurement Information System which looks at physical function, anxiety, depression, fatigue, sleep disturbance, pain, and ability to participate in social roles. The hope of this clinical trial is to determine whether stem cell therapies work to treat osteoarthritis and also which type of stem cell works best. The biggest strength of this clinical trial when it is complete will be that it was randomized unlike previous trials for stem cell therapy. The study also utilized participants with varying levels of osteoarthritis, so hopefully there will be different grades in each group to determine if one type of stem cell has more of an effect on a specific grade of osteoarthritis.

These case studies can yield some new conclusions while others are still left to be determined. The clinical trial under the Japanese Regenerative Medicine Act is important because it is the first trial to be supported by the government. It also yields results to show the medical community that stem cell therapy does decrease pain for those struggling with advanced osteoarthritis. Both the clinical trial done in Australia and the one done in Canada looked at dosage of stem cells which builds on the previous clinical trial. The Australian clinical trail

found that the best intervention in their study was the two injections 6 months apart for Grade II to Grade III osteoarthritis. The Canadian clinical trial concluded that the best intervention in their trial was the highest dose of stem cells, 50 million cells, for severe osteoarthritis (Grades III to IV). Both studies concluded that the stem cells did not fully heal the knee joint, but instead seem to take a more supportive role to assist the cells to decrease inflammation and limit pain. Lastly, the new clinical trial starting in the United States will hopefully yield results as to which stem cells are most effective for treating osteoarthritis in the knee.

Cost

Currently, if an individual wanted to receive stem cell therapy for osteoarthritis in the United States, the individual would apply to be a candidate at one of the stem cell clinics around the country (Figure 5). Treatments at the stem cell clinics vary as there is no standard treatment right now. For example, a clinic in Panama requires a 4-day treatment which includes a physical examination and blood testing followed by 3 intravenous injections of mesenchymal stem cells and intracellular injections if needed (Riordan 2017). This is very different from a clinic in Boston which considers the treatment an outpatient treatment as it only takes a few hours after the stem cells have been harvested and says the patient can walk within 24 hours (Boston Stem Cell Center, 2019). Stem cell therapy is not currently covered by insurance in the United States because it is not approved by the FDA, though it is in the clinical trial phase now, which is the last step before potential approval (FDA, 2019). Out-of-pocket costs often determine whether an individual can try a new medical technology. When using a stimulated patient of a 57-year-old male, the average cost for the 273 clinics which offer stem cell therapy was $5,156 (Piuzzi et al, 2018). The range of costs was between $1,150 to $12,000 for clinics which provided same day unilateral stem cell knee injection. The average clinical efficacy was 82.2% with a range of 55%

to 100% (Piuzzi et al, 2018). If stem cells proved to be effective for treating a certain stage of osteoarthritis and if the effects were long term, then stem cell therapy would be more cost efficient than a total knee replacement.

Side Effects/Concerns

Unfortunately, there are some potential risks associated with stem cell therapy for osteoarthritis. One of the major problems is that these stem cells are often cultured *in vitro*. In vitro culture can modify cellular characteristics which could form harmful viruses. There is currently no standardization, so quality of stem cell preparations varies greatly between suppliers increasing the risk of modified stem cells being used (van der Kraan, 2013). The second risk is a risk of unwanted tissue formation. A rabbit study using adipose-derived mesenchymal stem cells showed that several weeks after the injection, the mesenchymal stem cells were found both in the affected joint but also in other locations such as the thymus and gastrointestinal tract (van der Kraan, 2013). It is a fear that the migration of these cells to other locations of the body could result in unwanted calcifications at sensitive sites in the body which would lead to severe medical complications such as bone formation in the heart. A severe complication of using mesenchymal stem cells is that mesenchymal stem cells migrate towards tumor sites already in the body. Mesenchymal stem cells have been shown to support tumor invasion and metastasis (van der Kraan, 2013). It is a fear that the mesenchymal stem cells would become a source of nutrients for cancer cells to grow with, though, so far this appears to be an uncommon phenomenon in humans (van der Kraan, 2013). This aspect of safety is important for the FDA verification process.

Conclusion

Osteoarthritis is the most common joint disease in our society due to the rising elderly and obese populations. Individuals who suffer from osteoarthritis face crippling joint pain due to degradation of the cartilage in their joints. There is currently no cure for osteoarthritis. There are several temporary treatments such as anti-inflammatory medications or total knee replacements for those at the end stages of the disease. These treatments each have shortcomings, however, that make them less than ideal. Medications have dangerous side effects, so individuals cannot remain on them forever. A total knee replacement does fix the knee joint, but it also limits mobility. Most individuals cannot return to sport after a total knee replacement meaning that usually only individuals over 60 years old opt for this treatment. There are many individuals under 60 years old who need treatment who fall into this treatment gap. These individuals have very limited options. These individuals are the most important reason that stem cell therapies for osteoarthritis need to be further discussed. Stem cell therapy may allow individuals to continue to lead active lifestyles because the joint could be repaired.

So far stem cell therapy does not yield conclusive results as to if it is more beneficial than a total knee replacement for everyone. Not all stem cell therapy being offered today is beneficial for all patients. In fact, some treatments can be harmful to individuals seeking treatment. The FDA warns individuals to ask questions before receiving treatment such as whether the treatment is FDA approved or if it is being studied under an Investigational New Drug Application which is a clinical trial submitted to the FDA (FDA, 2019). The FDA also warns about therapies approved in other countries. It is imperative that the individual read the countries' policies and ask questions to ensure that the treatment is safe (FDA, 2019).

Warnings aside, stem cell therapy does appear to be a promising solution for the future. To start, there are no ethical issues because the stem cells come from within the individual- whether it be bone marrow or adipose tissue. This is important because for a long time the only stem cells being used for treatment were from an (unborn) fetus. Second, if stem cell therapy was approved and insurance covered part of the treatment, stem cell therapy would be very cost efficient. The procedure itself is between $37,000 to $44,000 cheaper than a total knee replacement (Table 1). Stem cell therapy, according to current studies, appears to also involve less rehabilitation care after the procedure. The stem cell therapy required about four weeks of quadriceps exercises while a total knee replacement requires about four months of physical therapy. The only drawback is that current evidence seemingly concludes that stem cell therapy might be more beneficial for mid-stage osteoarthritis rather than end-stage osteoarthritis like a total knee replacement. Future work should follow those who have had successful stem cell therapy for mid-stage osteoarthritis to determine how long the treatment works or if an individual would need a total knee replacement later in life anyway. It would also be useful to find a dosage of stem cells that are the best for the treatment to be effective. This is important to standardize the treatment, so it would more easily be approved by the FDA.

With these findings, Julia and Henry still have decisions to make about what to do about their osteoarthritis. Julia is a younger adult who still wants to remain active. She is also young enough that she might outlive a knee replacement. At her age, Julia does not have Grade IV osteoarthritis, but rather, she has a Grade II or III osteoarthritis diagnosis. Julia would benefit most from the stem cell treatment. Julia is healthy besides her osteoarthritis, so she has no precursors for not being able to receive the treatment. Her main problem is the increased pain that keeps her from being active. Pain is what the stem cells have been proven to decrease in

every case study. With stem cell therapy, Julia could be back to being active with little knee pain a few weeks after treatment opposed to waiting almost a year after a knee replacement. My advisement would be for Julia to try stem cell therapy from a reputable stem cell clinic which she can determine by asking the FDA.

Henry is a different case than Julia. Henry is an older adult who is also overweight. Henry has not been active for 20 years. Henry has developed ulcers previously from taking anti-inflammatory medications. Henry also has Grade IV osteoarthritis. The stem cell therapy has not proven to be as effective for the later stages of osteoarthritis because the stem cells do not do the healing of the joint themselves. The recovery for Henry would not be easy, but I would suggest him receiving a knee replacement. He will most likely not outlive the knee replacement, and it is a proven treatment. His weight is still a lot of added pressure to a knee joint, so the stem cells might not be as effective for relieving pain. Henry would have to be diligent and go to his physical therapy to regain as much knee movement and function as possible. It would not matter to Henry as much if he is unable to run or participate in sport again. He would potentially start walking if he can which would still be beneficial for his health.

Figures

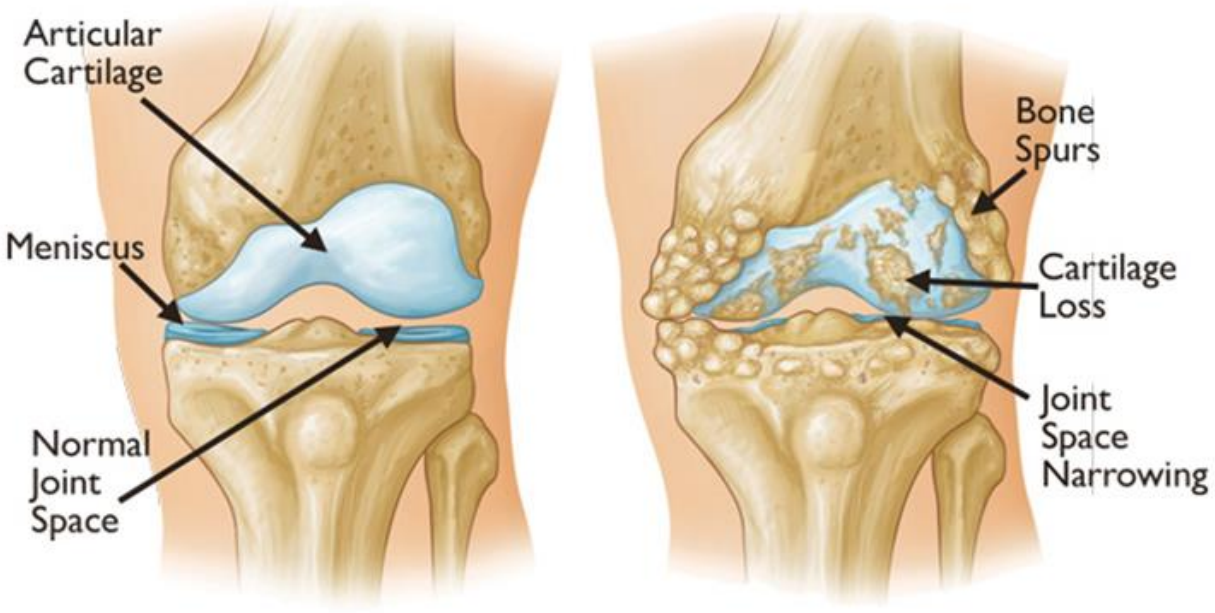

Figure 1: Comparison of Knee Joints: The left image shows a normal knee joint. Notice the coverage of articular cartilage over the entire surface of the femoral condyles (lower projections of the femur bone). There is a gap between the femur and tibia in the healthy joint. The right image shows a knee joint affected by osteoarthritis. Notice the articular cartilage is broken and does not cover the femoral condyles. There is no joint gap, so the bones grind together. There is also formation of bone spurs on both the femur and tibia.

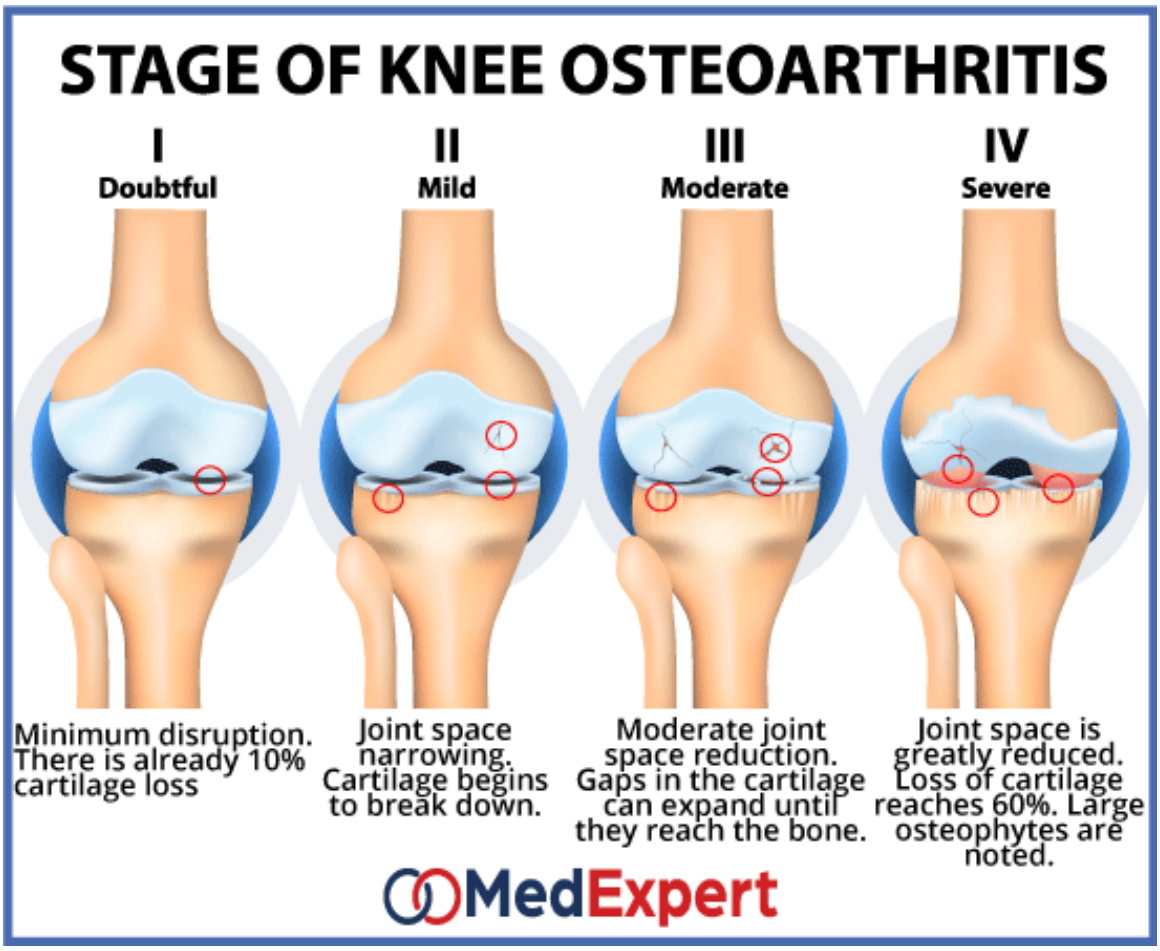

Figure 2: Kellgren-Lawrence Osteoarthritis Scale: The image shows the progression from a normal knee joint on the left to a severely affected knee joint on the right. Notice the change in cartilage between each knee. The leftmost picture shows an intact cartilage that surrounds the whole joint to cushion the bones. The second image shows a slight narrowing of the joint space as well as the development of osteocytes. The third image shows cartilage breaking down and cracking as it becomes thinner. In the fourth image, there is very little cartilage remaining and the joint space has narrowed, so the bones rub against each other.

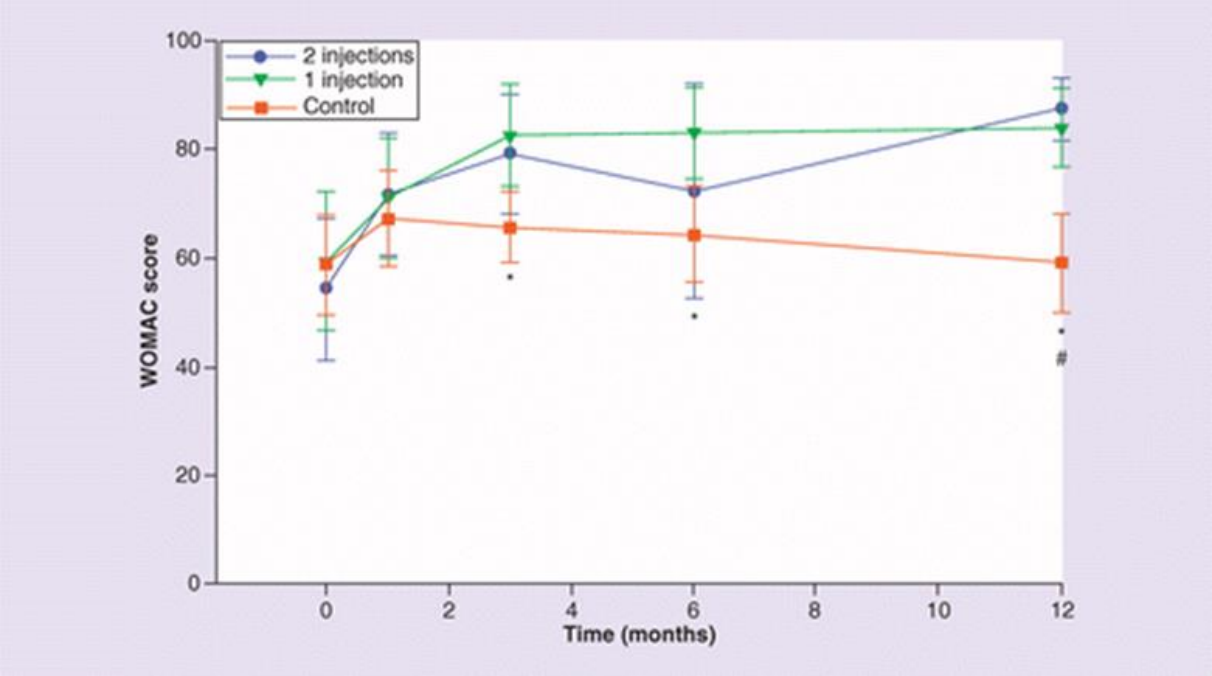

Figure 3: Global Western Ontario and McMaster Universities Arthritis Index (WOMAC) score. There was an improvement from baseline for both the one injection and two injection group. The baseline for one injection was 59 and it increased to 84 while the baseline for two injection was 54 and it increased to 87. An increase in score insinuates less pain and stiffness of the knee. Improvements were shown from 1 month to 12 months after injection.

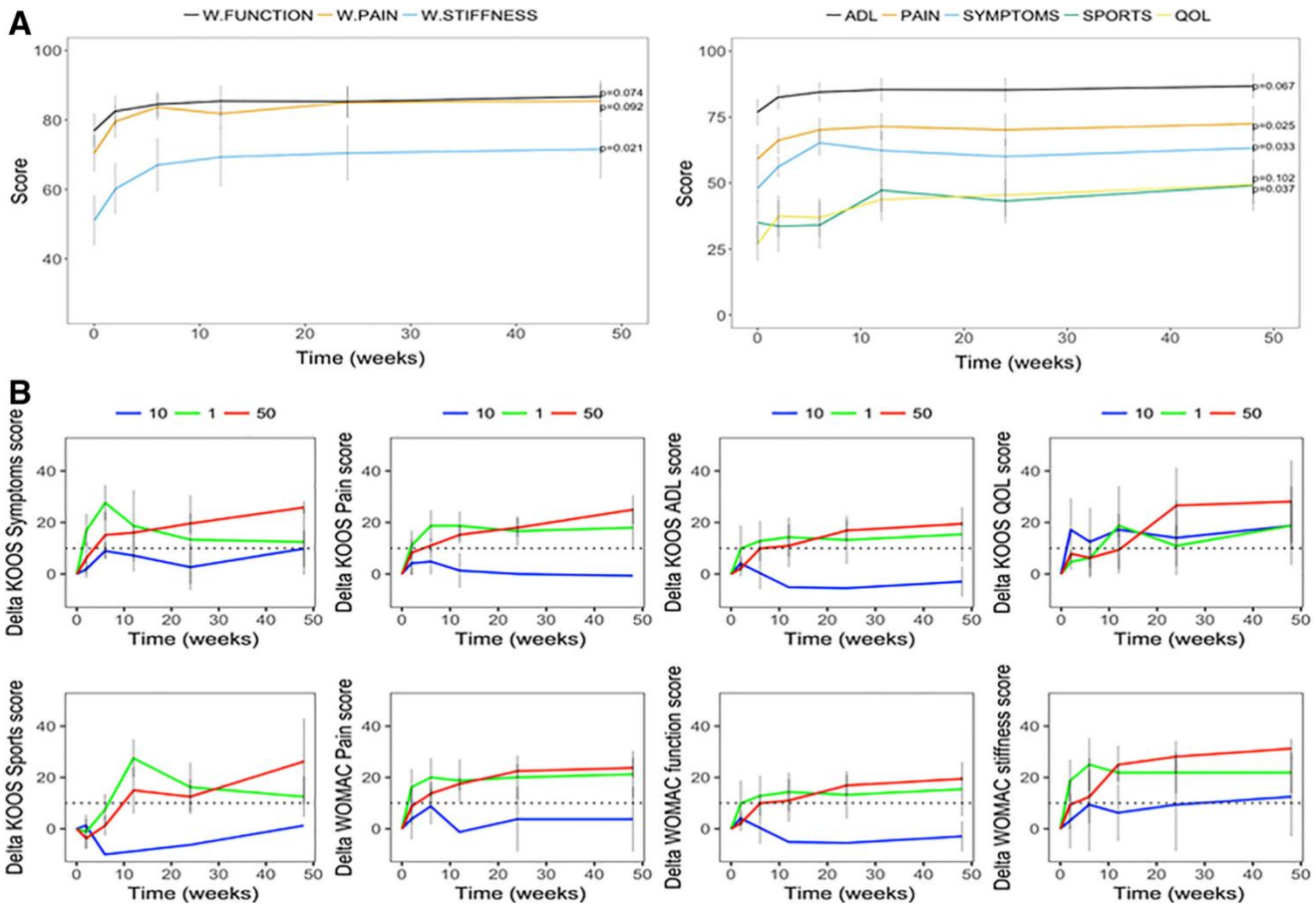

Figure 4: Patient Reported Knee Injury and Osteoarthritis Outcome Score (KIOOS) and Western Ontario and McMaster Universities Index score (WOMAC). (A): The WOMAC score is on the left divided into its 3 subcategories- Function, Stiffness, and Pain. The KIOOS score is on the right divided into its 5 subcategories- Activities of Daily Living, Pain, Symptoms, Sports, and Quality of Life. (B): The breakdown of each subcategory to show how participants in each injection dosage responded. The dotted line is the line of clinical significance which is an increase of 10. The green line is the 1 million cell dosage. The blue line is the 10 million cell dosage. The red line is the 50 million cell dosage.

Cost	Total Knee Replacement	Stem Cell Therapy
Procedure	$49,500	$5,156*
Inpatient	$7,500	N/A
Other	PT, follow-up, loss of work salary, house accomodations	Limited PT

Table 1: Cost Comparison of Total Knee Replacement and Stem Cell Therapy. The total knee replacement will cost about $57,000 before physical therapy, follow-up appointments, and loss wages because the individual cannot work. Stem cell therapy costs an average of 5,156, but there is a range of $1,150 to $12,000 depending on the clinic one chooses to go to. There also could be inpatient charges if the clinic is not an outpatient treatment facility. (* denotes that cost is not set due to differing treatments)

Figure 5: Patient results after stem cell therapy. This patient, who received treatment from a stem cell clinic in Indiana, shows increased joint space after stem cell therapy. The left image shows the knee before the stem cell therapy. The joint space was very limited. The right image shows the knee 8 months after stem cell therapy. The joint space increased drastically. The knee moves with less friction after the stem cell therapy.

Bibliography

AAOS. Total Knee Replacement - OrthoInfo - AAOS. (2019). Retrieved from https://orthoinfo.aaos.org/en/treatment/total-knee-replacement/.

Bellamy N, Campbell J, Welch V, Gee TL, Bourne R, Wells GA. (2006) Viscosupplementation for the treatment of osteoarthritis of the knee. Cochrane Database of Systematic Reviews, Issue 2. Art. No.: CD005321. DOI: 10.1002/14651858.CD005321.pub2.

Boden, S. D. (2019, January 28). Multicenter Trial of Stem Cell Therapy for Osteoarthritis (MILES) - Full Text View. Retrieved from https://clinicaltrials.gov/ct2/show/NCT03818737.

Boston Stem Cell Center. (2019). Stem Cell Injection & Therapy for Knee Pain. Retrieved from https://www.bostonstemcell.com/conditions-treated/stem-cell-treatment-for-knee-pain/.

Brigham and Women's Hospital (BWH). Knee Replacement Surgery. (2019). Retrieved from https://www.brighamandwomens.org/orthopaedic-surgery/knee-replacement-surgery.

Chahal, J., Gómez-Aristizábal, A., Shestopaloff, K., Bhatt, S., Chaboureau, A., Fazio, A., … Viswanathan, S. (2019). Bone Marrow Mesenchymal Stromal Cells in Patients with Osteoarthritis Results in Overall Improvement in Pain and Symptoms and Reduces Synovial Inflammation. *STEM CELLS Translational Medicine*. doi: 10.1002/sctm.18-0183

Chapman, K., & Valdes, A. M. (2012). Genetic factors in OA pathogenesis. *Bone, 51*(2), 258-264. doi:10.1016/j.bone.2011.11.026.

Da Costa, B. R., Reichenbach, S., Keller, N., Nartey, L., Wandel, S., Juni, P., & Trelle, S. (2017). Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of

osteoarthritis pain: A network meta-analysis. *The Lancet, 390*(10090). doi:10.1016/s0140-6736(17)30701-8.

De Bari, C., & Roelofs, A. J. (2018). Stem cell-based therapeutic strategies for cartilage defects and osteoarthritis. *Current Opinion in Pharmacology, 40*, 74-80. doi:10.1016/j.coph.2018.03.009.

FDA. (2019, September 3). FDA Warns About Stem Cell Therapies. Retrieved from https://www.fda.gov/consumers/consumer-updates/fda-warns-about-stem-cell-therapies.

Fransen, M., & Mcconnell, S. (2008). Exercise for osteoarthritis of the knee. *Cochrane Database of Systematic Reviews*. doi:10.1002/14651858.cd004376.pub2

Freitag, J., Bates, D., Wickham, J., Shah, K., Huguenin, L., Tenen, A., … Boyd, R. (2019). Adipose-derived mesenchymal stem cell therapy in the treatment of knee osteoarthritis: a randomized controlled trial. *Regenerative Medicine, 14*(3), 213–230. doi: 10.2217/rme-2018-0161

ISSCR. Types of Stem Cells. (2019). Retrieved November 3, 2019, from https://www.closerlookatstemcells.org/learn-about-stem-cells/types-of-stem-cells/.

Khan, M., Adili, A., Winemaker, M., & Bhandari, M. (2018, January 22). Management of osteoarthritis of the knee in younger patients. *CMAJ: Canadian Medical Association Journal*, *190*(3), E72+.

Kraan, P. M. (2013). Stem Cell Therapy in Osteoarthritis: A Step Too Far? *BioDrugs, 27*(3), 175-180. doi:10.1007/s40259-013-0017-6.

Lopa, Silvia, Colombini, Alessandra, Moretti, Matteo, & Girolamo, Laura de (2018). Injective mesenchymal stem cell-based treatments for knee osteoarthritis: From mechanisms of

action to current clinical evidences. *Knee Surgery, Sports Traumatology, Arthroscopy*.doi:10.1007/s00167-018-5118-9.

Losina, E., & Katz, J. N. (2012). Total knee arthroplasty on the rise in younger patients: are we sure that past performance will guarantee future success?. *Arthritis and rheumatism, 64*(2), 339-41.

Mehrabani, D., Mojtahed Jaberi, F., Zakerinia, M., Hadianfard, M. J., Jalli, R., Tanideh, N., & Zare, S. (2016). The Healing Effect of Bone Marrow-Derived Stem Cells in Knee Osteoarthritis: A Case Report. *World Journal of Plastic Surgery*, *5*(2), 168–174.

Messier, S. P., Gutekunst, D. J., Davis, C. and DeVita, P. (2005), Weight loss reduces knee-joint loads in overweight and obese older adults with knee osteoarthritis. Arthritis & Rheumatism, 52: 2026-2032. doi:10.1002/art.21139.

Niinimaki, T., Eskelinen, A., Mann, B., Junnila, M., Ohtonen, P., & Leppilahti, J. (2012). Survivorship of high tibial osteotomy in the treatment of osteoarthritis of the knee. *The Bone and Joint Journal*. doi:10.1302/0301-620X.94B11.29601

Piuzzi, N., Ng, M., Chughtai, M., Khlopas, A., Ng, K., Mont, M., & Muschler, G. (2017). The Stem-Cell Market for the Treatment of Knee Osteoarthritis: A Patient Perspective. *The Journal of Knee Surgery*, *31*(06), 551–556. doi: 10.1055/s-0037-1604443

Riordan, N. H. (2017, June 25). Stem Cell Therapy for Osteoarthritis. Retrieved from https://www.cellmedicine.com/stem-cell-therapy-for-osteoarthritis/.

Sardana, V., Burzynski, J., & Zalzal, P. (2016). Safety and efficacy of topical ketoprofen in transfersome gel in knee osteoarthritis: A systematic review. *Musculoskeletal Care*, *15*(2), 114-121. doi:10.1002/msc.1163

Scudellari, Megan (2016). How iPS cells changed the world. *Nature, 534*(7607), 310-312. doi:10.1038/534310a.

Shane Anderson, A., & Loeser, R. F. (2010). Why is osteoarthritis an age-related disease?. *Best practice & research. Clinical rheumatology*, *24*(1), 15-26.

Turner, M. L. (2011, March 11). Joint adventures: The path to total knee replacement. Retrieved from https://www.americannursetoday.com/joint-adventures-the-path-to-total-knee-replacement/.

University of Utah Genetic Science Learning Center. (2014, July 10) Stem Cells in Use. Retrieved November 28, 2018, from https://learn.genetics.utah.edu/content/stemcells/sctoday/

Vincent, T. L., & Watt, F. E. (2018). Osteoarthritis. *Medicine*, *46*(3), 187-195. doi: 10.1016/j.mpmed.2017.12.009.

W-Dahl, A., Robertsson, O., Lidgren, L., Miller, L., Davidson, D., & Graves, S. (2010). Unicompartmental knee arthroplasty in patients aged less than 65. *Acta orthopaedica*, *81*(1), 90-4.

Wang, Y., Yu, D., Liu, Z., Zhou, F., Dai, J., Wu, B., Zhou, J., Heng, B. C., Zou, X. H., Ouyang, H., … Liu, H. (2017). Exosomes from embryonic mesenchymal stem cells alleviate osteoarthritis through balancing synthesis and degradation of cartilage extracellular matrix. *Stem cell research & therapy*, *8*(1), 189. doi:10.1186/s13287-017-0632-0

Yokota, N., Yamakawa, M., Shirata, T., Kimura, T., & Kaneshima, H. (2017). Clinical results following intra-articular injection of adipose-derived stromal vascular fraction cells in patients with osteoarthritis of the knee. *Regenerative Therapy*, *6*, 108-112. doi:10.1016/j.reth.2017.04.002

Zhang, Y., & Jordan, J. M. (2010). Epidemiology of osteoarthritis. *Clinics in geriatric medicine*, *26*(3), 355-69.