

Stem Cell & Regenerative Therapies for Meniscus & Osteoarthritis of the Knee

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INTRODUCTION:

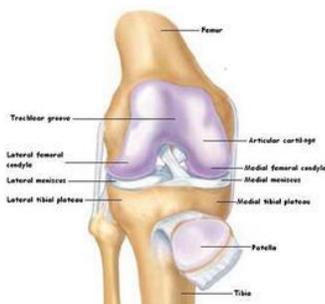
Osteoarthritis (OA) is not a disease of just cartilage but bones and bone marrow below cartilage. It is also involves the membranes around the knee and ligaments. Knee osteoarthritis is commonly viewed as the final common pathway for aging and injuries of joints. Because of medical advances the population of the world is growing older and the average life expectancy is extended, leading to an increase in the incidence of osteoarthritis of the large joints. Osteoarthritis is already one of the 10 most disabling diseases in developed countries. Osteoarthritis (OA) presents a major clinical challenge to most clinicians. Articular cartilage defects within the knee are common among the elderly population causing pain, reduced function and significant disability in affected patients. There is a poor capacity for “self prepare” of cartilage defects making management rather difficult. Current treatment emphasizes on reducing pain, maintaining mobility and minimizing disability. Regardless there has been until recently no therapies available that have the potential of regenerating the affected tissue.¹



According to the Agency for Healthcare Research and Quality more than 600,000 knee replacements and 285,000 total hip replacements are performed each year in the US. The demand for repeat joint replacement or revision of the previous joint replacement will double in the next 10 years. As the demand for joint replacement surgery increases the supply of orthopedicsurgeons performing this procedure are on the decline which may lead to a demand crisis.² Many individuals have lived active and healthy lifestyles that have preserved their health except they suffer from orthopedic problems such as osteoarthritis of the knees and hips, dramatically affecting the quality of their life. If we have enjoyed success we want to live, run, jump, play golf, walk on the beach and enjoy an active life through our senior years. Research and development efforts are underway worldwide in the field of regenerative orthopedic medicine to provide alternatives for treatment of osteoarthritis and degenerative joint disease.

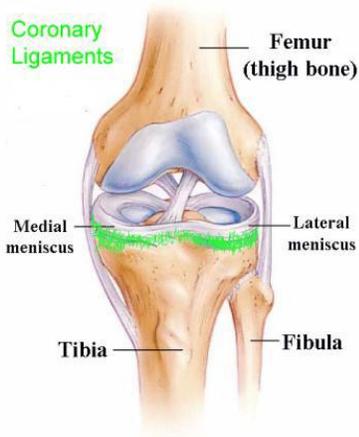
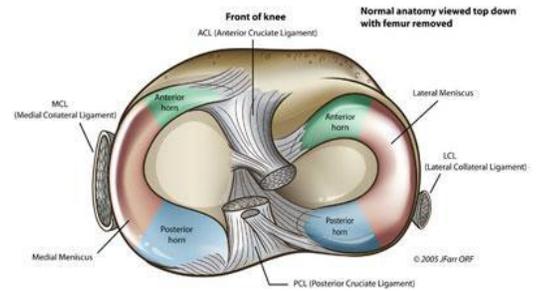


BASIC KNEE ANATOMY:



We are going start with some basic knee anatomy for those who may not be familiar with the knee. We are going to be making a number of references in this article to anatomical parts of the knee that we will need to be familiar with. We are not going to do a detailed review, but there are several keep points that we want to cover. An important part of knee anatomy that we will be referencing is the hyaline cartilage coving the end of the bone which is colored purple in the picture to the right. This area is representative of the “articular cartilage” that overlies the end of the bone. There is also a similar layer of cartilage on the under surface of the knee cap (patella) and the top of the tibia as well. The articular

cartilage that covers the surface of the patella is thicker than most areas in joints and will be an important point of discussion later in this article. There are also some additional cartilage structures in the knee which is the medial and lateral meniscus shown in the picture below on the left. The femur was removed in order to look down on the meniscus in the picture below to the left. Notice the moon shaped meniscus. Since the meniscus is shaped like a horn we call the part from the anterior horn and the part of the back the posterior horn. This region and the posterior horn are important because this is the most common location for tears and early wear and tear. Most individuals that have undergone surgery for meniscus tear will have undergone the surgery for a tear in this region. The posterior aspect of the meniscus takes a lot of torque and pressure and therefore wears down very easily. The meniscus is attached to the bone on the periphery by small short ligaments called “coronary ligaments” that I have colored in green in the picture on the picture to the left. The small short ligaments are a very important target for injection therapy in regenerative injection procedures.

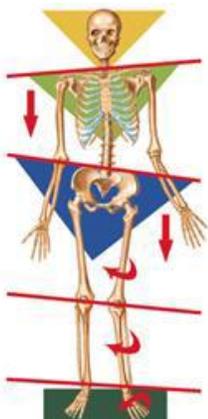


One of the very first “regeneration” procedures that I personally began using over 25 years ago was the use of “prolotherapy” which I have discussed in the article entitled “Regenerative Injection Therapy in Pain Medicine” that you can find on this website. Prolotherapy utilizes typically natural substances such as dextrose sugar directed to the ligaments which causes a fibrous connective tissue proliferation which help strengthen ligament and connective tissue attachments. In fact there are other ligaments of the knee that are also important targets for prolotherapy injections. We will not spend a great deal of time discussing the various ligaments of the knee, but it is important to discuss how critical these structures are in supporting and stabilizing the knee joint and how important they are as a target for physician specializing

in regenerative injection therapies. Many years ago my primary method of treatment of knee injuries and osteoarthritis was utilizing dextrose based injection solutions directed to the various ligaments of the knee. We found this to be empirically speaking to be helpful in many patients with knee pain and arthritis. Today the technology of regenerative medicine has advanced and we now are able to provide a whole host of different treatment strategies that are can be more effective.

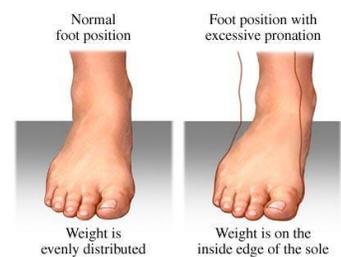


Before we begin to explore treatment of the knee with stem cell therapies we need to cover a couple of critical topics. Before we begin to explore treatment of the knee with stem cell therapies we need to cover a couple of critical topics. The first is to address some of the important stress that is placed on the knee that causes the knee to degenerate in the first place. If you do not deal with the mechanical stressors that are breaking down the knee it is more difficult to maintain improvement once it is accomplished. We will discuss 2 important topics that are the major contributors to the stress applied to the knees with walking. This first is the foot and ankle. The shape of your foot and ankle is critically important and governs the function of your foot during walking and can apply variable degrees of stress to the knee and lower extremity with walking.



FOOT PRONATION:

Foot pronation is a natural motion of the foot however an individual who excessively pronates places excessive stress throughout the lower extremity hip and pelvis. The picture to the right demonstrates a foot in excessive pronation. As the foot pronates the tibia and femur excessively internally rotate placing undue torque on the knee. This causes malalignment of the kneecap which causes excessive wear of the articular cartilage in the joint as well as wear on the meniscus.



This also places excessive tension on the previously described coronary ligaments and other important ligaments of the knee. This contributes to the wear and tear that ultimately can lead to osteoarthritis.



OBESITY:

Obesity has been shown to be a significant risk factor in development of osteoarthritis of the knee.³ The increased mechanical forces and weight bearing of the joint is probably the primary factor leading to joint degeneration. Individuals who are obese also have an abnormal angulation to the knee worsening the compression force on the cartilage and causing malalignment of the kneecap. This results in increased joint reactive forces in the inside compartment of the knee accelerating degeneration.⁴

Obesity and osteoarthritis is a vicious cycle. The worse the arthritis becomes the more pain and reduced activity tolerance an individual has. The less activity the more obesity and the cycle continues. Many individuals become so functionally disabled they can hardly move and then seek our care for stem cell therapies and other regenerative interventions. Many of these individuals have already been offered a total joint replacement. These individuals often expect a cure for their condition and come in for stem cell therapies expecting they can experience this cure. They have made many attempts at diet and weight loss but in the end they have made little change. Stem cell therapies may provide some symptomatic relief and may even offer a means to allow them to become at least more physically active but if the weight does not come off the disease will progress. Despite the great potential of moderate regenerative therapies the mechanical forces on the joint will cause deterioration of articular cartilage. An important part of disease management will be weight loss. Stem cell therapy will not be the answer. Many individuals say if you fix my knees I can walk and loose weight. Unfortunately, that strategy may not be effective, and efforts will need to be undertaken for dietary and lifestyle changes to loose weight and then all forms of treatment can be more effective.



THE EFFECT OF MENISCUS THE SURGERY ON ARTHRITIS PROGRESSION:

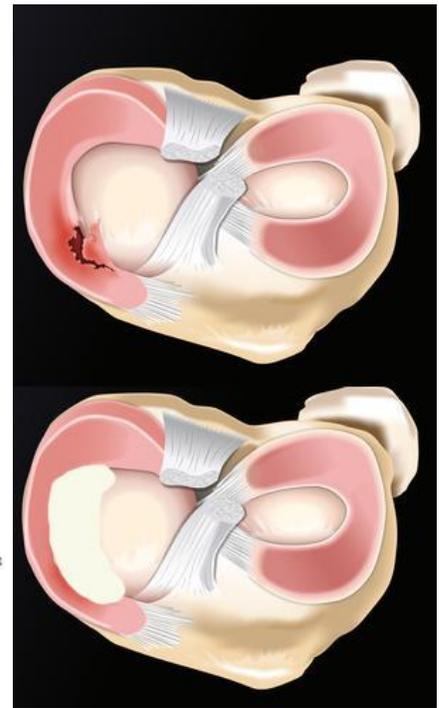
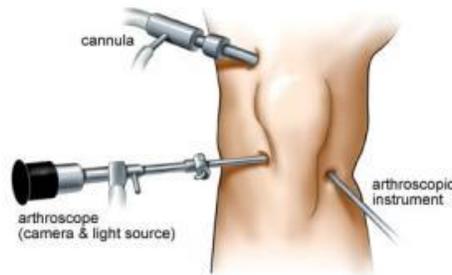
Many individuals with osteoarthritis have a previous history of a damaged meniscus where an arthroscopic procedure was done to remove part of the torn cartilage. It has been known for a long time that removal of damaged meniscus or cartilage from the knee substantially increases the risk of progression of joint failure.⁵⁻⁷ The picture to the right demonstrates atypical meniscus tear above and the colored portion below represents a typical pattern what portion of the meniscus would be removed by the surgeon to eliminate the tear. This type of surgical procedure does lead to short-term benefit but orthopedic research scientists are beginning to question the value of this procedure. When a portion of the meniscus is removed it increases the surface contact area and perpetuates a more rapid progression to osteoarthritis. We have known this for many years.⁸⁻¹⁰ For example Dandy in 1975 described problems with breakdown in the cartilage of the kneecap, overlying the femoral condyle, retained meniscus fragments and other issues following arthroscopic meniscectomy.¹¹ Katz and his numerous colleagues published last year an article in the New England Journal of Medicine demonstrating the patients with meniscus tears had similar outcomes whether or not they underwent arthroscopic surgery or simply physical therapy.¹² In individuals over 50 years of age 35% have meniscus tears that can be incidentally discovered and are asymptomatic.¹³ One must then ask how important is the finding of a meniscus tear? Another important point is that individuals with osteoarthritis frequently have meniscus tears which we will discuss later in this paper.^{14,15} So, the question is what we do with individuals with meniscus tears with or without osteoarthritis present?

Recently a study was published which evaluated patients receiving either “sham arthroscopic surgery” compared to arthroscopic debridement of cartilage and showed that the debridement procedure was no better or equivalent to a placebo procedure in improving the pain and self-reported function.¹⁶ In addition post procedural follow-up demonstrated the objective function was worse in the debridement group than the placebo group!¹⁶ With mounting evidence that arthroscopic procedures may not be the answer to meniscus lesions there is going to be a need for advancing technology and alternatives to arthroscopic surgery and debridement of the meniscus or debridement procedures for osteoarthritis.

WHAT IS OSTEOARTHRITIS?

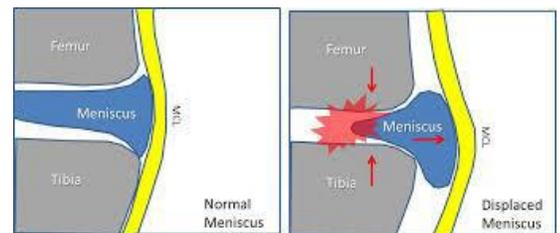
Before we discuss the treatment of osteoarthritis of the knee with current regenerative medicine technology including stem cell therapy we need to look carefully at the pathology of osteoarthritis.

Osteoarthritis of the joint can have multiple causes. There are individuals who are into their 90s with no signs of clinical or functional problems of the disease. And we can see individuals in their 30s with advancing arthrosis and functional disability. One possible source is injury to or breakdown of ligaments.



An example would be the 38-year-old which MRI is noted to the right. At the asterisk on the MIR image you may notice more light-colored signal indicating edema in the bone from a cruciate ligament injury and the meniscus on the inside (medial) knee is extruding out of the joint from injuries to supportive ligaments running alongside the knee. This phenomenon of displacing of the meniscus is relatively common. The picture to the left provides a simple graphic representing a meniscus displacement caused by injury to a critical ligament that anchors the meniscus to the bone.

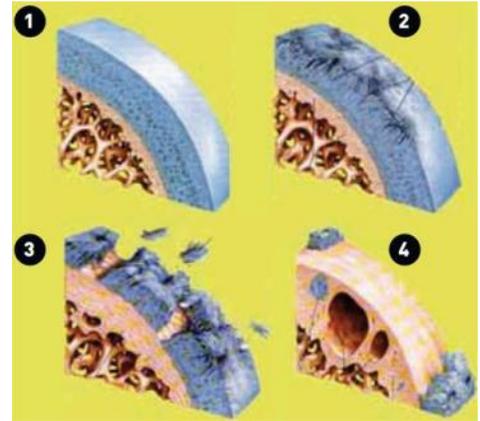
Meniscus extrusion can be a cause of joint space narrowing which has been largely overlooked. Although standard x-rays may show evidence of joint space narrowing it will not demonstrate the meniscus displacement. This finding can only be seen on ultrasonography or MRI.¹⁷ When we see this particular disorder we find the knee to be more problematic to treat. If the decision is made to attempt to treat this needs to be done with a combination of special connective tissue grafting at the meniscus root and along the parameter of the meniscus in conjunction with wearing a knee brace for 6 weeks. Noncompliance with the knee brace can result in treatment failure.



The meniscus does not need to be displaced to cause progressive osteoarthritis. Studies have shown that tears in the posterior horn of the meniscus can cause dynamic changes in the function with abnormal loading resulting in progressive osteoarthritis.^{18,19} Researchers have proposed that the small coronary ligaments previously described attached to the meniscus (ligaments of Humphrey and Wrisburg) may play an important role in osteoarthritis progression.²⁰ It is for this reason that we will commonly include injections around the perimeter of the knee within these ligaments.

As previously described in our anatomy section the bone within the joint is covered by “articular cartilage”. The bone directly underneath the cartilage is called “subchondral bone” which means the bone under cartilage. The bone under the cartilage has a shock absorbing property which is essential for protecting the overlying cartilage from damage.²¹

In the picture above on the right the articular cartilage is represented in Gray. Over time articular cartilage begins to erode away from bone and the bone under the cartilage has many adaptive changes including bone edema, etc. which can be seen on MRI. As bone under cartilage begins to thicken it loses its property for shock absorption and cartilage protection.²¹



As cartilage cells erode from bone they float in the synovial fluid and then stick to the membrane around the knee. This membrane is called the “synovial membrane”. Typically this membrane’s role is to secrete lubricating fluid that nourishes articular cartilage.²² Special cells in the synovial membrane secrete not only substances used for lubrication and nutrition of cartilage but also contain immune cells that can respond to foreign antigens. Small molecules of necrotic cell material and fragments of degenerating cartilage can activate the immune response resulting in inflammation and thickening of this membrane and result in pain and swelling.²³ It is this

inflammation that is linked to both initiation and progression of osteoarthritis.²⁴ The fluid in the joint becomes full of these harmful substances that contribute to the breakdown of the joint. Within the inflammatory fluid secreted by the immune cells are contained metalloproteinases (MMP) that destroy cartilage further. A recent advanced in orthopedic science is the development of a technique to isolate a protein from your blood called alpha-2-macroglobulin. This protein can be isolated from your blood buy a laboratory technique and injected into your knee. We are currently using this technique with or without stem cell and we’ll be monitoring clinical outcomes over the course of next year. We believe it could represent another important regenerative medicine tool for the treatment of osteoarthritis.

Part of the critical component of treating osteoarthritis is using a stem cell technique that can “reset” and alter this significant inflammatory response within the joint that secrete numerous chemicals that damage the articular cartilage and produce pain. Stem cells often work by dampening the immune/inflammatory response.²⁵⁻²⁷ It is important to understand that while steroids do cause reduction of inflammation they are damaging to your articular cartilage. Part of the inflammatory pathway involved in osteoarthritis and pain is inflammatory substances mediated by chemicals called “cytokines”. These “cytokines” unfortunately besides causing inflammation can induce cartilage cells to produce



enzymes and inflammatory substances that drive the destruction of the cartilage cells and cartilage architecture.²⁸ Obviously it is important to target this pathologic process with treatment that is going to be effective. Steroids offer a very short-term improvement in joint inflammation. Stem cells produce an autoimmune regulatory response and release of regulatory proteins with the potential of some regenerative capacity and seems to be more practical approach to managing the symptoms of osteoarthritis. Autologous stem cells. Therefore taken from your body could potentially provide a means of targeting these destructive cytokines chemicals.

MRI has basically replaced the conventional use of x-ray in diagnosing the various pathologies involved in osteoarthritis.^{29,30} A common surgical practice today is to use a technique called “microfracture”. This is a method whereby under arthroscopic surgery the surgeon will drill holes in the bone overlying the areas that

cartilage has eroded away as shown in the picture to the right. The idea is to let the bone bleed and induced stem cell repair and replacement of articular cartilage. Although this has shown some short-term benefit this technique has not shown any significant improvements with long-term results,³¹ Once again we find common methods of treatment used today that fall short and again provide a strong impetus to search for alternatives. We are currently utilizing some techniques that may offer promise for certain types of full-thickness articular erosion. We discuss these techniques when appropriate at the time of our consultation and review of your MRI.

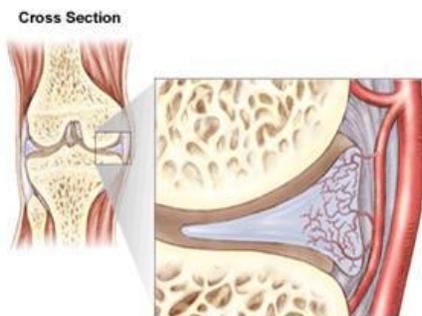
INTRODUCTION TO STEM CELL & REGENERATIVE THERAPIES FOR ARTICULAR CARTILAGE & OSTEOARTHRITIS OF THE KNEE.



Over the last decade, there has been a rapidly advancing fund of knowledge utilizing creative laboratory techniques to prepare autologous cell preparations for the purpose of regenerative therapy in orthopedic conditions. Although we are still restricted from cell culture and expansion by the FDA, many of these newer techniques which are FDA compliant, are beginning to emerge that are showing efficacy in treatment of soft tissues such as, ligaments, tendons, joint injuries and degenerative disease.

We will reference adult mesenchymal stem cells (MSCs) throughout the article. Mesenchymal stem cells are found in a number of locations such as bone marrow, fat, and even blood. Mesenchymal stem cells are cells that have the potential to become many other types of cells when exposed to specific growth factors or environments. Our interest is in the cells for osteoarthritis and their ability to differentiate into cartilage lineage which can be a great potential for cell-based articular cartilage repair.³²⁻³⁴ Articular cartilage within an individual's knee has a limited repair capacity on its own. The application of mesenchymal stem cells have the potential of healing damage to meniscus tissue and is currently being studied extensively.³⁵ These mesenchymal stem cells have the properties of “developmental plasticity” which means they can change to other tissues when placed in the right environment.^{36,37} Fat cells and its associated connective tissue can be used as a “scaffolding” for stem cells. We utilize this technique extensively when repairing rotator cuff tears and other orthopedic injuries.

One of the big problems with meniscus tears in the knee is where the injury to the meniscus is located. If you notice on the picture to the left there is a section of the meniscus which has good blood supply and there is a section of the meniscus that does not. We often refer to these 2 zones as the “red zone” and the “white zone” of the cartilage. For years my predominant concern has been whether or not a tear exists in the “red zone” or the “white zone” of the cartilage. If patients would have red zone tears I typically would treat them with regenerative injection therapies including stem cell and if they had a white zone tear I often referred the patient to surgery. Today this is a much more difficult decision in lieu of emerging research on the potential benefit of stem cell therapies and problems associated with arthroscopic meniscectomy as we have already discussed. We still have more questions and answers with stem cell therapies. We still need to conduct studies extending over several years and tracking and quantifying articular cartilage recovery following stem cell injection procedures. This will hopefully answer the question as to whether or not individuals in the future should treat various articular cartilage injury conservatively reserving surgical intervention for specific cases.



WHAT IS THE RESEARCH TO SUPPORT CARTILAGE AND ARTHRITIS IMPROVEMENT?

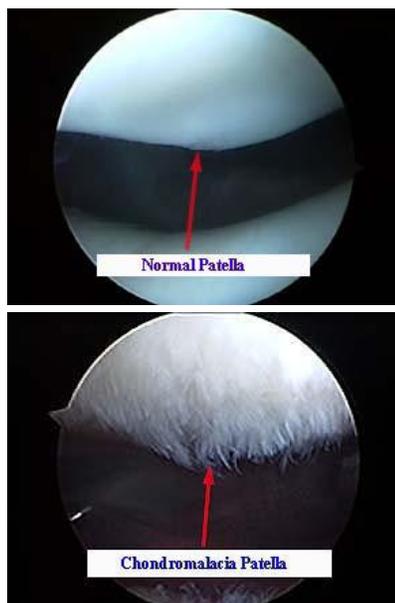
Studies are beginning to emerge demonstrating the production of an abundance of extracellular matrix proteins and substances that cartilage cells make located in sites were stem cell injections are performed specifically in the avascular zone of the cartilage.³⁸⁻⁴¹ This is encouraging but still does not provide us complete answers. A lot of the research being conducted present time involve the use of implantation of a scaffolding device embedded with stem cells.⁴² The use of implantable scaffoldings embedded with stem cells is still in early infancy and requires further research before this can be approved by the FDA and implemented in clinical practice. Current clinical outcomes research however is encouraging. Once again we desperately need long-term outcome studies that we will be participating in over the course of the next 3 years. In addition this will require repeat MRI studies and on certain cases possibly even a second look with arthroscopic procedures.

Believe it or not there has been arthroscopic second look research that has been done! In other words physicians have injected autologous stem cells after arthroscopic inspection of the joint and lavage with saline⁴³. After stem cell injection surgeons went back and reevaluated the knee under arthroscopic surgery to evaluate whether or not there was improvement. Almost all patients showed significant improvement in all clinical outcomes of follow-up. All of the patients in this study improved at 2 years compared to the 12 month follow-up! 87.5% of elderly patients greater than 65 years of age (14 out of 16) improved or maintained cartilage status at least 2 years postoperatively. More importantly none of these patient underwent total knee arthroplasty (joint replacement) during the 2 year follow-up.⁴³ The type of stem cell therapies utilized in this study was a technique called “stromal vascular fraction” utilizing stem cells from fat.

It is always more complicated when the patient has been seen for potential treatment who has already undergone 2 or more previous arthroscopic debridement procedures in the knee and now presents with progressive worsening arthritis and pain. These patients will demonstrate rapid progression of osteoarthritic disease, and ultimately culminating in a total joint arthroplasty procedure. The question is what to do with these patients. Is there research to support the possible beneficial effect of mesenchymal stem cells delivered via injection to the knee in these patients? Actually yes there is. For example a study done by C. Thomas Vangsness, Jr. and his colleagues demonstrated that after stem cell injection and patient’s having undergone arthroscopic meniscectomy there was increased meniscus volume determined by MRI in much more patients in the study then those injected with Synvisc-like injections which are often the most commonly offered treatment after arthroscopic failure. This study demonstrated that there was evidence of meniscus regeneration and improvement in knee pain after stem cell injection and that there may be some protective effects of the stem cell injection treatment. This does not mean that every patient who undergoes a stem cell injection after a failed arthroscopic surgery is going to benefit! People who are undergoing stem cell injection therapies need to realize that the treatment can fail.

CHONDROMALACIA PATELLA:

One of the frustrating conditions that I have been working with for 30 years in practice is what to do with patients who have pain under the kneecap and degenerative changes in the articular cartilage under the kneecap. Over time early arthritis of the patellofemoral joint can occur because of obesity, foot pronation, misalignment of the kneecap for many reasons including muscular strength and imbalance, etc. The cartilage begins to wear. The top picture on the right demonstrates a normal smooth articular cartilage surface under the kneecap. Notice the picture on the bottom that demonstrates a fragmentation of the articular cartilage that makes it look like “crab meat”. This is what softening and breaking down of the cartilage appears like. This causes symptoms of crepitation and grinding noises under the kneecap with squatting, ascending and descending stairs and movement of the knee.

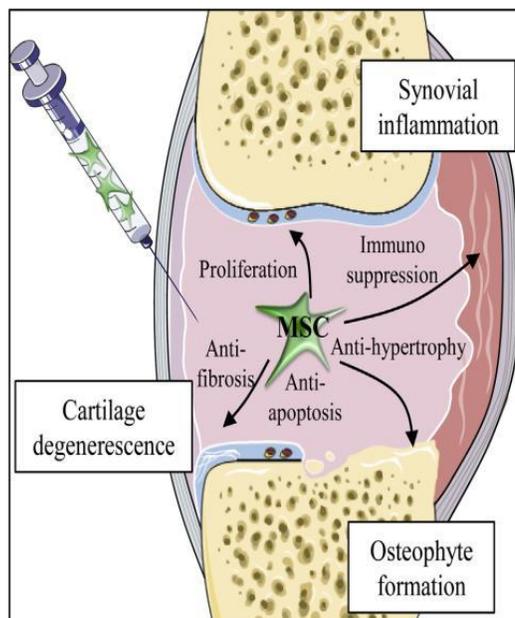


We use the term “chondromalacia patella” which basically means a softening of the cartilage under the kneecap. Once this cartilage becomes fragmented the cartilage begins to erode until areas of bone are showing and arthritis progresses. Besides orthotic correction, exercise, physical therapy, etc. I have used various regenerative strategies including PRP injections. More recently stem cell injection techniques are beginning to be utilized for this condition. In a recent study one month after injection of autologous adipose derived stem cells patient’s pain improved 50-70% and after 3 months patient’s improved 80-90% and continued to improve over 1 year.⁴⁴ More importantly the MRI findings demonstrated recovery of the articular cartilage.⁴⁴ I have had an opportunity to meet this research and discuss his findings in this study and the methods he used to obtain the results. It is certainly encouraging. Since I have not encountered other techniques except for stem

cell injections that could potentially create a significant beneficial effect in a single treatment. These cellular interventions may provide the ability to treat both acute trauma to prevent cartilage loss or long-standing degenerative changes much more effectively in the future. We desperately need more research to continue to develop this technology and to do research on long-term clinical outcomes.

WHY DO I WANT STEM CELLS IN MY KNEE?

Autologous stem cells have been shown to protect cartilage cells in osteoarthritis against cell death and progression of degeneration.⁴⁵ Even though osteoarthritis is not considered an inflammatory arthritis like rheumatoid arthritis, there are still pro-inflammatory chemicals which include cytokines, metalloproteinases, reactive oxygen species which are present in osteoarthritis joints. These pro-inflammatory cytokines are down regulated in the presence of autologous stem cells.⁴⁶ In addition to adipose derived stem cells having significant anti-inflammatory effects bone marrow derived stem cells have similar anti-inflammatory effects of osteoarthritis.⁴⁷ Therefore injection of adipose derived stem cells or bone marrow derived stem cells has a number of beneficial effects in osteoarthritic joints which include inhibition of bone spur formation (osteophyte), decreased synovial inflammation, reduced cartilage degeneration with less fibrosis and cartilage cell death as well as stimulation of proliferation of cartilage cells and secretion of extracellular matrix important as a component of cartilage production.^{47,48} In traumatic injuries of joints intra-articular injection of bone marrow derived stem cells have demonstrated that it can prevent the development of posttraumatic arthritis.⁴⁹ As I have stated before additional studies of also shown that injection of mesenchymal stem cells from bone marrow demonstrated its relative safety with improved pain, functional status in knee pain following injection and MRI studies of these patients demonstrated increased cartilage thickness and decreased subchondral bone (bone below the cartilage) reduction in edema and half the patients.⁵⁰ Research has also shown that regardless of whether it is bone marrow derived or adipose tissue derived stem cell preparations produce protective effects of cartilage cells from death and degeneration.⁴⁵

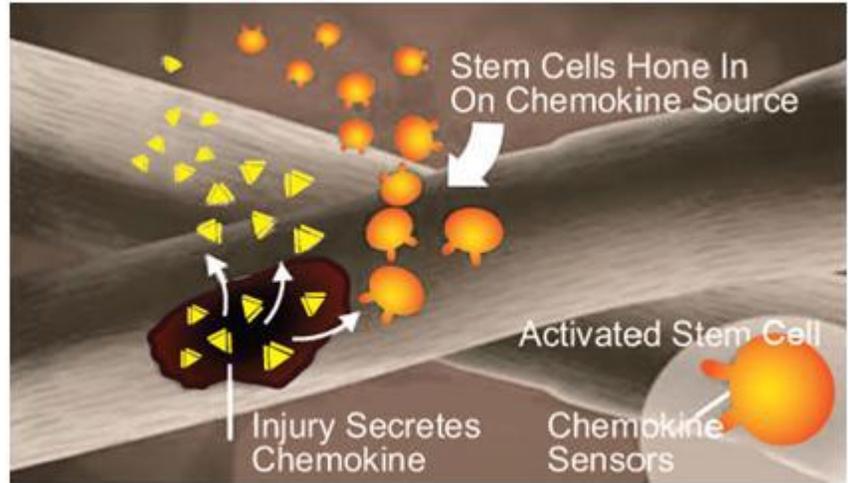


MSC

In conclusion, this is just beginning of the new revolution and therapeutic interventions not only for orthopedic application but for many disease processes. Autologous stem cell therapy is probably going to revolution the treatment of arthritis and the treatment of joint injuries. More research obviously needs to be done and the technology advanced.

HOW DOES A STEM CELL KNOW WHERE TO GO?

One of the most fascinating parts of moderate stem cell therapy is our understanding of cell “homing”. Stem cells “home” to injured tissues!⁵¹⁻⁵³ Activated stem cells express certain receptors on the surface of the cell that are sensitive to chemicals secreted by inflamed and injured tissues. These chemicals are called chemokines. There are special small proteins that are secreted in the area and circulate around your body that tell a stem cell where to go. Studies have been done where the stem cell have been “tagged” with the radioisotope so that it could be tracked like a homing beacon. When stem cells are injected via IV one can see that they accumulate in the area of a focal inflammation. This is the process we call “homing”. Typically stem cells are injected and at the focal site of local injury but can also be given IV. In our practice because we focused more on orthopedic conditions we use ultrasonography to place stem cells in a precise location of tissue injury.



STEM CELLS CONTROL INFLAMMATION:

One of the important observations and discoveries that we noticed when first utilizing autologous stem cells was the rapid improvement that some patients experience with inflammation and pain in arthritic joints. We had grown accustomed to having some patients undergo significant post injection flare following areas regenerative injection procedures. After utilizing autologous stem cells the first thing we noticed was how rapidly some patients start to feel better. There are other individuals where the response to injection is delayed and improvement does not occur for several months. For those who experienced rapid improvement. This effect is probably more related to the profound effect on inflammation and immune system.⁵⁴⁻⁵⁶ In fact the profound effects on inflammation and immune function is why stem cells are currently now being looked at for treating not only osteoarthritis but also rheumatologic disorders such as rheumatoid arthritis and autoimmune conditions.^{57,58} In fact the anti-inflammatory and immune mediated responses caused by autologous stem cells is showing promise in the treatment of conditions such as multiple sclerosis.⁵⁹

Stem cells and the many supportive cells that are found with them maintain a homeostatic environment which promotes growth and regeneration. For those interested in the biochemistry of the autoimmune effects of stem cell therapy I briefly discussed some of the autoimmune effects of stem cells below which include its properties and ability to suppress inflammation through the secretion of mediators including IL-10⁶⁰, IL-17⁶¹, TGF-B superfamily⁶², LIF⁶³, soluble HLA-G⁶⁴, and IL-1 receptor antagonist.⁶⁵ In addition the expression of immune regulatory enzymes such as cyclooxygenase⁶⁶, and, indolamine 2,3 deoxygenase⁶⁷ are seen which help cells “take” to the area and promote regeneration. The cells induce generation of “T regulatory cells” which have a profound effect on the local inflammatory environment. T Regulatory cells (Treg).⁶⁸

Stem cells are capable of directly suppressing the immune systems inflammatory response by depleting certain inflammatory cells (T cells).⁶⁹ Because stem cells expressed CD34 receptors they may play a “Immunosurveillance” role for circulating CD34+ cells in circulation via activation and differentiation of these cells into dendritic cells (DC) via of toll-like receptors (TLR) agonists.⁷⁰

Although this is a complex subject and part of this article is written for those who have a science background or who are interested in the biochemistry the important concept here is that there is a profound effect on a inflammation in a local environment such as a joint or soft tissue.

WILL STEM CELL INJECTION CURE MY ARTHRITIS?



Let us start by saying there is NO CURE for osteoarthritis. But, as technology advances we are getting better at managing it. There are many stem cell applications for various knee injuries and arthritic conditions. For example one may have a osteochondral defect such as what is shown a picture to the right. This is a focal area of articular cartilage that has either been injured and lifted off the bone or has been worn off. Orthopedic physicians have been working for years on various techniques to try and heal these osteochondral defects with various surgical transplantation procedures, etc. Over the last several years we have adopted specific stem cell techniques that have been shown to be quite effective in treating these focal osteochondral defects.

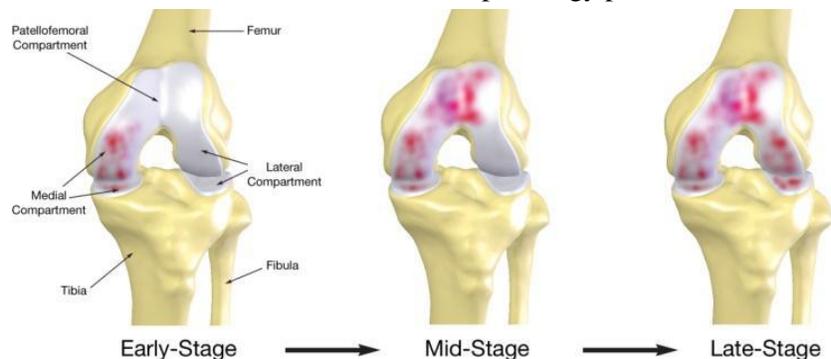
We believe that we have reached a point where we no longer have to be dependent on arthroscopic surgical procedures and microfracture techniques to try and heal these lesions.

We are usually not so lucky to just see a simple focal osteochondral defect presented to us. Typically it is much more common for an individual who seeks our care to much more severe degenerative arthritic disease. Clearly, the less extensively arthritic disease, the better options for management. We typically obtain MRI studies to stage the arthritic disease and determine all of the various degenerative pathologies that may be at play in an individual’s knee.

Current stem cell technology is not a method that provides a “cure for arthritis”. Stem cell therapies may be an important method to manage osteoarthritis. Osteoarthritis is a progressive degenerative disease with no known cure. Even knee replacement surgery is not a cure, but another effective tool in management of pain and disability. A knee replacement can buy significant time with improved pain and function, but eventually the surgical implants can fail and an individual can be facing revision surgery. Many individuals choose to try more conservative means to either try to prevent undergoing surgical intervention or delay of surgery if possible.

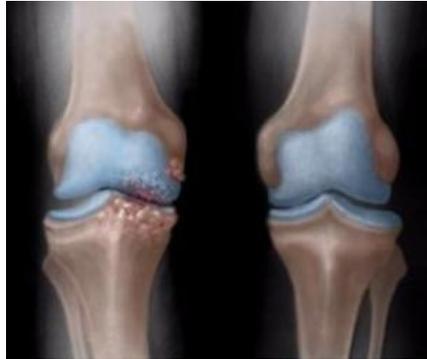


Some individuals find periodic stem cell injections provide sufficient enough pain relief that they are quite satisfied and using this method to manage the disease. Clearly, total joint replacement surgery may be the best option for treating some individuals. The specific regenerative medicine procedures, and stem cell procedures must be customized to the individuals needs and the clinical pathology presented. This requires a comprehensive history, physical examination, including ultrasonography exam and review of MRI studies to make specific decisions about whether or not there is a chance that an individual may benefit. Part of this process is to determine what structures of the knee had degenerated such as



the meniscus and articular cartilage and the degree and severity of that degeneration. This consultation process also reviews the various biomechanical factors that may be contributing to the degenerative disease that may be able to be altered or controlled.

WHAT TO EXPECT FROM A STEM CELL THERAPY PROCEDURE:



Your experience with stem cell procedures will vary depending on where you have the treatment. Most facilities offering stem cell procedures typically use one particular method that they favor. The most dominant stem cell technique utilized worldwide is bone marrow derived stem cell. There are still facilities that offer adipose tissue derived STEM cell therapy, which is called stromal vascular fraction. We found in our personal experience both of these techniques to be helpful in certain cases. We have abandoned the use of adipose tissue stromal vascular fraction in hopes that the FDA will eventually come out with a position statement as to whether or not physicians in the United States can continue to use this method. There are still facilities around the US offering this

method of treatment. We have been developing numerous technologies that we believe is the best choice for regenerative injection procedures in the US at this time. We have an article on this website entitled “beyond stem cell therapy” that provides information in regards to what to expect if you decide to seek stem cell procedures involving bone marrow procedures or adipose tissue derived procedures. We refer to that article that also has some details about the mechanisms of how these treatments may work. We are fortunate to be working some of the best stem cell and regenerative medicine experts in the country as part of our physician Consortium nationwide. Many of the techniques we utilize our proprietary to this organization throughout the country and we will be very happy to share with our patients a multitude of choices if a decision has been made to seek our care.

IN SUMMARY:

Current methods of stem cell therapies utilized today represent great progress with the treatment of osteoarthritic disease of the knee. We are taking painstaking efforts to try to document outcomes that we can make the best decisions and choices of various regenerative injection therapies. There is still a great deal of research and development. That will be needed in the future in order to constantly improve outcome.

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