



## Stem Cell And Regenerative Therapies For Hip Arthritis And Related Disorders

By Michael N. Brown, DC, MD, DABPMR-PAIN. Reprinted with permission.

### INTRODUCTION:

Hip pain associated with osteoarthritis is the most common form of hip pain in older adults.<sup>1</sup> Prevalence of hip osteoarthritis ranges from 0.4% to 27%<sup>2-4</sup> Osteoarthritis (OA) of the knee however is more common than the hip.<sup>5</sup> We will discuss two broad categories of osteoarthritis of the hip. The first is primary osteoarthritis where we do not have a known cause and secondary osteoarthritis. Secondary OA of the hip occurs secondary to some condition which could be previous trauma, biomechanical stress or problems causing a breakdown in the hip, previous congenital problem in the hip such as dysplasia, and a host of other problems.<sup>6</sup> Advancements in medical science and technology are allowing us to live longer and therefore with growing life expectancy it is expected that we are going to see a higher incidence of arthritis of large joints. At present this represents the baby boomer population. Osteoarthritis presents a challenge to all clinicians, especially osteoarthritis of the hip. Osteoarthritis of the hip can lead to significant pain and functional disability. It is becoming commonplace for the American public to simply assume that if you get osteoarthritis you simply go have a “hip replacement”. 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 not been, until recently, any therapies available that have the potential of regenerating the affected tissue.<sup>7</sup>

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 orthopedic surgeons performing this procedure are on the decline which may lead to a demand crisis.<sup>8</sup> Individuals in the “baby boomer” population may have enjoyed success and lived healthy lifestyles with few medical problems that would slow them down except orthopedic problem such as hip osteoarthritis. They want to enjoy their success and walk on the beach, play golf, play tennis, and enjoy the fruits of the labor only to be disabled and have chronic pain from osteoarthritis of the hip. And more often than not it is typically not just a single joint causing disability such as the hip but a myriad of orthopedic problems which include back pain, neck pain, knee osteoarthritis, etc. Over just the last few years we have entered a new area of regenerative orthopedic medicine where alternatives to surgical procedures are now an option.

### BASIC HIP ANATOMY... WHERE IS THE PAIN COMING FROM?

We began our discussion with a brief review of hip anatomy. It is important to point out that the hip joint is a ball and socket joint and the top of the femur is capped with an important hyalin cartilage colored in pink in the picture to the right. This cartilage is of critical importance. It is the corrosion of this articular cartilage that heralds the arthritic condition of the hip. The femur has large bony protuberances utilized for powerful muscle attachment. The largest of these bony protuberances is the greater trochanter which is labeled in the picture to the left.

The greater trochanter is actually a very important part of hip anatomy and we will also be referencing multiple soft tissues that attach to the hip at the greater trochanter throughout this article. As one can see in the picture to the right there are multiple muscles that attach onto or around the greater trochanter.

Some of these muscles generate tremendous force and when injured or inflamed can cause significant pain and disability. The hip joint is quite mobile and because of this mobility there can be friction between all of the muscle and tendon attachments to the hip. To eliminate this friction we have bursa dispersed between tendons or between tendons and bone to reduce friction. Imagine taking a deflated balloon and placing several drops of oil within the balloon and tying the top of the balloon off. As you now hold the balloon between your hands and rub your hands over the balloon the oil inside the balloon lubricates its inner surface and reduces friction. This anti-friction device created by the balloon is exactly how a bursa works. A bursa is a thin sac where a small amount of lubricating fluid is contained within it. These are dispersed under tendons and between tendons and bone throughout your hip. There can be as many as 20 bursa dispersed around the hip. The picture to the right demonstrates just a few. The most important two bursa of the hip is the greater trochanteric bursa and the bursa underneath the gluteus medius tendon or better known as the gluteus medius bursa. It is common place for these two bursae to become inflamed and irritated with chronic stress to the hips soft tissues resulting in significant hip pain. It is actually much more common to have pain from the tendons, muscles and bursa of the hip than it is to have arthritis pain of the hip.

Typically if I were to see 10 individuals with hip pain, 9 of those individuals would have pain from the muscles, tendons and bursa and only 1 would have pain from arthritis. It is also very common for individuals to be misdiagnosed in regards to the source of their hip pain. I have had individuals come in for a stem cell consult for hip arthritis and much to their surprise they were not in need of stem cell therapy for an arthritic hip but had pain primarily secondary to a problem associated with muscles, tendons and bursa. Directing the appropriate treatment improves their condition without treating any hip arthritis condition. Diagnosis is critically important. Sometimes an individual may have an arthritic joint but it's not causing pain and the pain the individual is experiencing is from the soft tissues around the hip.

Another important structure of the hip is the "acetabular labrum". As we have stated the hip is a ball and socket joint. Around the socket portion of the joint there is a small cartilaginous rim, sort of like a gasket. This cartilage rim serves for ligamentous attachments and also helps deep in the joint. A tear of this cartilaginous rim can be quite painful and one of the common causes of persistent hip pain with or without arthritis is a acetabular labrum tear. We will discuss various congenital anomalies that can impinge on this rim and cause it to tear and breakdown early in life and can lead to osteoarthritis. We will discuss that a little later in this article.

#### REGENERATIVE INJECTION THERAPY "THE EARLY YEARS":

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 and pain medicine" that you can find on this website. Prolotherapy is a method of treatment whereby injections, typically of dextrose sugar, are directed to soft tissue attachments to bone such as ligaments, tendons, etc. These injections cause increase in collagen and connective tissue which strengthens weakened ligaments and improves degenerative changes in the tendon at the attachment to bone.

This technique of ligament and soft tissue regeneration dates back to the 1930s. Specially trained physicians eventually became skilled in the detailed evaluation, injection techniques and methods required to use this technique. Eventually a national Association was born (American Association of Orthopedic Medicine) and we began to see physicians specializing in "orthopedic medicine" rather than "orthopedic surgery". Orthopedic medicine practitioners specialize more in soft tissue regenerative techniques which has been the discipline I have been working in for years.

In 1993 I, a medical pathologist, and a veterinarian surgeon began doing animal research on the potential healing power of platelets that circulate in your blood. There are numerous important growth factors contained within platelets that have the potential for healing soft tissues and actually treating arthritis. We began developing methods for extracting platelets and growth factors and using thrombin proteins to treat the discs in the lumbar spine of animals. Later a

more simplistic form of this treatment was conceptualized by other physicians using simple centrifuge techniques and the popularity of this method exploded worldwide. Today we call this “platelet rich plasma”.

With a simple blood draw your blood can be centrifuged and processed in such a way to remove the red cells from your blood and the majority of your plasma, which is the fluid that your blood circulates in. We concentrate the platelets and once transferred to a syringe can be a “cellular transplant” that can be injected in ligaments, tendons, and within arthritic joints. Again, this has become extremely popular amongst physicians doing orthopedic medicine and orthopedic surgery. Once stem cell preparations began to be developed it was discovered that this same mixture of platelet concentrate, from your blood, is one of the critical steps in modern stem cell preparation and therapy. It turns out the growth factors contained in platelets are critical in driving the stem cells to repair articular cartilage and control inflammation. We had no idea back in 1993 that today the simple platelets that we were experimenting with would become a worldwide tool in modern day stem cell therapy. Several years after working with platelet rich plasma we then began to use the same centrifuge methods to centrifuge bone marrow blood. Bone marrow blood contains mesenchymal stem cells that are from a “lineage” that are capable of generating tissue repair such as cartilage, bone, ligament, tendon etc. We began to develop methods for enhancing spinal fusion surgeries, and use these cell preparations in various orthopedic applications. Years later we now have the technology that we will be discussing later in this document. However, before we get too far into the topic of modern day stem cell and regenerative therapies we need to address a number of issues that involve risk factors or factors that contribute to ongoing pathology around the hip.

One of the first things that a patient who consults with us for hip pain will notice is that when we initially evaluate the patient we actually evaluate their foot and gait biomechanics before we ever look at the hip. If you do not deal with the mechanical stressors that are breaking down the hip it is more difficult to maintain improvement once it is accomplished. This shape and structure of your foot and ankle is critically important because it can alter the mechanics of your foot during gait and apply stress to your ankle, shin, knee, and hip during gait if the structure is not correct. Abnormal foot function leads to stress on soft tissues that can ultimately lead to pathology and pain. Although we are not going to address the complex topic of biomechanics of the foot and ankle, I do want to address one thing that I always have problems with “over-pronation”.

#### 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 (shin) and femur (thigh) excessively internally rotate placing undue torque on the hip and the various muscles, tendons and ligaments of the hip. The additional stress caused by this over-pronation causes degeneration of tendon attachments and ultimately can lead to chronic pain from tendonosis and bursitis of the hip. This may well cause an abnormal wear and tear to articular cartilage leading to arthritic changes.

Because of this we take painstaking efforts to evaluate an individual's foot structure, function and gait to determine if there are simple measures that we can take to correct this and take the stress off the hip. We feel it is critical to resolve this problem so that any improvements made by our regenerative therapy interventions have a better chance of providing long-term improvement.

#### OBESITY:

Of course we need to also cover the subject of obesity. Interesting enough obesity is a much stronger risk factor and much more problematic in the osteoarthritis of the knee than hip. Although obesity is a strong risk factor for the incidence of new onset hip osteoarthritis it may not cause the rapid progression of disease like it does in the knee.<sup>9</sup> Regardless of the epidemiology research, one of our therapeutic goals is to reduce mechanical forces and weight bearing on the joint and therefore we believe that obesity contributes to this.

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 will continue. Many individuals become so functionally disabled that 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 therapy expecting a cure for the hip pain. They then expect that after their cure they will be able to become physically active with their new found cure and then they can work on the lifestyle changes, exercise, lose weight and do all the other things that set this is a psychologic to begin with. These individuals have made countless attempts at diet and weight loss but “at the end of the day” they have made little change. The truth of the matter is that although stem cell therapy may provide symptomatic relief and may even offer a means to allow them to become at least more physically active 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. Although the deterioration may be slower with stem cell therapies it still is going to progress without aggressive measures taken to lose weight. Therefore individuals with significant osteoarthritis and obesity require much more comprehensive management than simply stem cell and regenerative intervention.

To my surprise there has been no significant association between running and the progression of osteoarthritis in 3 epidemiology studies.<sup>10-12</sup> Although we are not going to do a comprehensive discussion of all risk factors including nutrition, it has been found the low levels of vitamin D can cause worsening of arthritis.

I do want to point out that if an individual does undergo a hip replacement surgery, obesity or high body mass index (BMI) is associated with a need for subsequent total hip arthroplasty.<sup>13</sup> In other words if you have a hip replacement and you are obese you're at higher risk for having to have a revision by breaking down the replacement.

#### FEMORAL ACETABULAR IMPINGEMENT AND HIP ARTHRITIS:

Femoral acetabular impingement (FAI) represents an abnormal contact between the anterior acetabular rim and the femoral neck at the waist. The picture on the top left demonstrates a normal spherical femoral head. The head of the femur then tapers into the neck of the femur. This tapering and the spherical head glides within the socket extremely well in a normal hip. If one has a “bump” or cam shaped femoral head as shown in the top right, mid abnormal contact or impingement can occur when you flex your hip.

Other methods of impingement would be an abnormal overhang causing a pincer type effect as shown in the bottom left. You can also have a combination of both shown in bottom right.

I commonly see this condition in athletic individuals who started having difficulties with groin pain and hip pain in their mid years of life. Individuals who were wanting to maintain regular athletic activities become frustrated with the persistent groin pain never realizing that they actually have a mechanical impingement syndrome that they were born with that is now beginning to break down the acetabular labrum and has started an early arthritic condition in their hip. There are other configurations of the abnormal anatomy of the hip such as acetabular retroversion, inadequate femoral neck anteversion, a non- spherical femoral head, and decreased offset of the head relative to the neck which we will not discuss in this article. It should suffice to say that there are a number of things that can occur that can be a “set up” for trauma to the acetabular labrum and can cause early arthritis of the hip. Individuals who have this problem gradually begin to experience restricted range of motion and often times begin to try to do deep stretching, lunge maneuvers, knee to chest maneuvers in an attempt to try to improve range of motion when in fact all they are doing is making the problem worse. These individuals can participate in athletic endeavors but need to restrict there in range movement in flexion and avoid movements that caused this impingement to prevent further damage.<sup>14</sup> Individuals who began to develop

osteoarthritic changes in the hip at a younger age often have underlying problems such as femoral acetabular impingement syndromes.<sup>15</sup>

We frequently encounter patients who have had long-standing impingement syndrome that has led to break down in the acetabular labrum and has led to early arthritic disease. These individuals are often much younger than you would expect for the development of osteoarthritis. Although there are some early surgical interventions to impingement many times by the time they see us the arthritic changes have become too advanced for the surgeon to do an arthroscopic procedure. This leaves them with persistent hip pain and no other treatment options. We have had relatively good success using a combination of bone marrow derived mesenchymal stem cells in addition to adipose derived stem cells in combination with PRP. More recently we have used adipose derived stem cells only in combination with PRP and have seen excellent success with this technique as well. Treatment of the arthritic changes and cartilage followed by some protective strategies to prevent further damage to the hip is typically our recommendation.

Another problem that we encounter with this patient population is those who have had arthroscopic debridement of the acetabular labrum and or shaving of the bone to relieve the impingement. Sometimes the surgery is very successful. Other times we have seen patients who have had slightly too aggressive shaving of bone and this has left the patient with instability of the hip joint and the actually feel worse. In these cases we have had some success with combining stem cell and prolotherapy or PRP injection techniques directed to the ligaments of the hip. These patients with surgical induced instability are quite complicated and have to be managed on a case by case basis.

#### WHAT IS OSTEOARTHRITIS?

Before we discuss the treatment of osteoarthritis of the hip with current regenerative medicine technology including stem cell therapy we need to look carefully at the pathology of osteoarthritis in this joint. Osteoarthritis of the joint can have multiple causes. Osteoarthritis is related to but not caused by aging. There are individuals who are into their 90s with clinical or functional signs of disease. And we can see individuals in their 40s with advancing arthrosis and functional disability.

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 cartilage has a shock absorbing property which is essential for protecting the overlying cartilage from damage.<sup>16</sup> In the picture above on the right the articular cartilage is represented in pink. Over time articular cartilage begins to erode away from bone, 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.<sup>16</sup> As cartilage cells erode away from bone they 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 nourished articular cartilage.<sup>17</sup> 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.<sup>18</sup> It is this inflammation that is linked to both initiation and progression of osteoarthritis.<sup>19</sup> The fluid in the joint becomes full of these harmful substances that contribute to the breakdown of the joint.

#### DEGENERATIVE CYSTS AND JOINT COLLAPSE:

A common pathologic process of osteoarthritis especially in large joints is a condition of degenerative cysts. As the articular cartilage erodes away from the surface of the bone it exposes the bone surface. Of course as I have previously stated small fragments of articular cartilage and debris flow in the joint and make contact with the membrane around the knee causing chronic inflammation and pain. As the cartilage begins to a road away from the surface of the bone and the bone surface is now exposed the fluid (synovial fluid) within your joint under weight bearing places pressure on the bone that is abnormal. The bone begins to remodel and

eventually an impression can be seen in the bone that gradually deepens until it forms a “cyst”. Sometimes the cysts are small and sometimes the cyst can be quite large. The x-ray on the left is a normal hip and the x-ray on the right is an arthritic hip with degenerative cysts and rather severe osteoarthritis.

Occasionally the degenerative cysts can become so large that they put the joint at risk for collapse and on occasion the head of the femur can collapse causing a deformity and a rapid worsening of osteoarthritis. Although some physicians will still offer patient’s stem cell therapy, in that given situation I typically recommend a hip replacement. If an individual has medical risk factors that prevent him from having hip surgery then stem cell therapies can sometimes make the patient more comfortable for periods of time but is certainly not going to solve any major problems.

#### AVASCULAR NECROSIS:

Avascular necrosis of the femoral head is a progressive disease that typically affects younger individuals. The blood supply of the head of the femur becomes disrupted leading to necrosis of bone. The bone can ultimately collapse leading to severe degeneration, pain and disability.<sup>20</sup> Typically this culminates in a hip replacement even in a younger individual. The exact cause of this condition is still not well understood but there are clearly risk factors.

#### RISK FACTORS:

- Corticosteroid use
- Alcohol abuse
- Radiation therapy
- Smoking
- Chronic renal failure
- Pregnancy
- Sickle cell disease
- Lipid disorders

There are actually many more risk factors. The earlier the diagnosis is made the more effective modern stem cell therapies are and the better the prognosis for individuals with this devastating disease. For most of my career when I have encountered this condition we have typically had to refer the individual for a hip replacement surgery. However there are rapidly emerging stem cell therapies being utilized for this condition today.<sup>21</sup> In AVN (avascular necrosis) there is insufficient supply of progenitor cells located in the femoral head and proximal femur to remodel the area of necrosis when this condition occurs.<sup>22</sup> For years we have been doing various orthopedic surgical procedures to try to help these individuals such as drilling the bone (core decompression) to try to reestablish blood supply the results have been disappointing.

In 2002 Hernigou and Beaujean first described technique for injecting mesenchymal stem cells combined with the bone drilling procedure.<sup>23</sup> They utilized the injection of mesenchymal stem cells derived from bone marrow and using a drill then introduced the stem cells into the area of necrosis. For those who had stage III and stage IV a more severe disease, about half still had to undergo total joint arthroplasty (hip replacement) and in the long-term most of these individuals also ended up with a hip replacement.<sup>23</sup> Over time the techniques of core decompression (drilling) and bone marrow stem cells began to show promise demonstrating the majority of the patients holding up even after 5 year follow-up.<sup>24</sup> Multiple studies were then published by a number of physicians and researchers looking at this technique. Eventually researchers became concerned about whether or not stem cells could survive in the area of necrosis.<sup>25,26</sup> Various refinements with improved stem cell counts and techniques have introduced techniques that have become more successful.<sup>21</sup> What we have learned is that it is important to catch the disease process as early as possible where stem cell therapies are much more successful. Utilizing this minimal invasive technique in combination with stem cells young individuals can typically avoid a joint replacement and return back to normal function.<sup>21</sup>

## STEM CELL THERAPY FOR PAIN AND INFLAMMATION ASSOCIATED WITH 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 secretes numerous chemicals that damage the articular cartilage and produce pain. As we will discuss adipose derived stem cells do exactly this by dampening the immune/inflammatory response.<sup>27-29</sup> It’s 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.<sup>30</sup> Obviously it is important to target this pathologic process with treatment that is going to be effective. Fortunately we believe based on a limited research and clinical outcomes that autologous stem cells taken and concentrated from your body provide a means of targeting these destructive cytokines chemicals. We now utilize MRI to monitor disease progression or regression with treatment. It is important to understand that MRI’s has basically replaced the conventional use of x-ray in diagnosing the various pathologies involved in osteoarthritis.<sup>31,32</sup>

A few years ago we entered a new era in regenerative medicine. Having spent my entire career utilizing various regenerative medicine technologies I began to see a significant change in the direction in this field. I started a stem cell company 6-7 years ago working with the umbilical cord derived stem cells and found that for the most part it was a dead-end, because we could not use most of the technology we were working on in the United States. We closed that company and began to change our focus. Over time I began to notice a paradigm shift in the stem cell science and research. The US began to fall behind in utilizing various stem cell strategies because of politics and federal government regulation, creative physicians and stem cell scientists turned to the use of “autologous” stem cell therapies. Autologous stem cells mean the stem cells were obtained from your own body and the cells are then transplanted back to your body for therapeutic application. Federal regulations currently still restrict the use of your own cells and we are unable to culture and expand cells and undergo significant “manipulation” of cells. Despite these limitations there are technologies and methods of using regenerative and stem cell therapeutic procedures especially in the field of orthopedics that have revolutionized the treatment of arthritis, articular cartilage, tendon and soft tissue injuries. This has led to the development of various sequential centrifugation techniques to concentrate autologous stem cells and create cell complex mixtures concentrated from fat and bone marrow derived cells primarily. It is taken several years and travel around the world comparing methodologies before I have finally arrived at the methods we now use.

We will reference adult mesenchymal stem cells (MSCs) throughout the article. Mesenchymal stem cells are found in a number of locations but we will be referencing cells that we obtain from your bone marrow and fat. 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 in the cells for osteoarthritis is their ability to differentiate into cartilage lineage which can be a great potential for cell-based articular cartilage repair.<sup>33-35</sup> Fibrocartilage tissue 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 articular cartilage tissue and is currently being studied extensively.<sup>36</sup> These mesenchymal stem cells have the properties of “developmental plasticity” which means they can change to other tissues when placed in the right environment.<sup>37,38</sup> 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.

### WHY DO I WANT STEM CELLS IN MY HIP?

Autologous stem cells have been shown to protect cartilage cells in osteoarthritis against cell death and progression of degeneration.<sup>39</sup> 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.<sup>40</sup> In addition to adipose derived stem cells having significant anti-inflammatory effects bone marrow derived stem cells have similar anti-inflammatory effects of osteoarthritis.<sup>41</sup> 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.<sup>41,42</sup> In traumatic injuries of joints, an intra-articular injection of bone marrow derived stem cells have demonstrated that it can prevent the development of posttraumatic arthritis.<sup>43</sup> As I have stated before additional studies have also shown that injection of mesenchymal stem cells from bone marrow demonstrated its relative safety with improved pain, functional status and pain following injection and MRI studies of these patients demonstrated increased cartilage thickness and decreased subchondral bone (bone below the cartilage) reduction in edema in half the patients.<sup>44</sup> Research has also shown that regardless of whether it is bone marrow derived or adipose tissue derived there are protective effects of cartilage cells from death in degeneration.<sup>39</sup>

In conclusion, we have been searching for decades for a method of treatment that could be a disease modifying agent that is cost effective, safe, and easily accessible. We have also been searching for a means to control the osteoarthritic process and try and prevent or slow down the breakdown of the articular cartilage over time. Autologous stem cell therapy is probably going to revolutionize the treatment of arthritis in all joints but especially the knee and hip. More research obviously needs to be done and the technology will continually improve.

#### 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!<sup>45-47</sup>

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. They 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 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.

#### STROMAL VASCULAR FRACTION & STEM CELLS CONTROL INFLAMMATION:

One of the important observations and discoveries that we noticed when first utilizing adipose derived stem cells was the rapid improvement that patients experience with inflammation and pain in arthritic joints. We had grown accustomed to having some patients undergo significant post injection flare, following areas that had regenerative injection procedures. After utilizing adipose derived stem cells the first thing we noticed was how rapidly patient start to feel better. It turns out that stem cells, especially those derived from adipose cells, have profound effects on inflammation and immune system.<sup>48-50</sup> In fact the profound effects on inflammation and immune function is why stem cells were currently now being looked at for treating not only osteoarthritis but also rheumatologic disorders such as rheumatoid arthritis and autoimmune conditions.<sup>51,52</sup> In fact the powerful anti-inflammatory and immune mediated responses caused by adipose derived stem cells is showing promise in the treatment of multiple sclerosis.<sup>53</sup>

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-10<sup>54</sup>, IL-17<sup>55</sup>, TGF-B superfamily<sup>56</sup>, LIF 57, soluble HLA-G<sup>58</sup>, and IL-1 receptor antagonist.<sup>59</sup> In addition there is expression of immune regulatory enzymes such as cyclooxygenase<sup>60</sup>, and, indolamine 2,3 deoxygenase<sup>61</sup> 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).<sup>62</sup>

Stem cells are capable of directly suppressing the immune systems inflammatory response by depleting certain inflammatory cells (T cells).<sup>63</sup> Because stem cells express 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.<sup>64</sup>

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 inflammation in a local environment such as a joint or soft tissue.

#### WHAT KIND OF STEM CELL THERAPY DO WE PROVIDE IN THE US?

There are actually many types of stem cell therapies that have become available worldwide. There are many stem cell procedures that are completely unavailable in the United States because of FDA regulations. We are working right now with the national organization of stem cell researcher’s and a stem cell network of physicians that we have developed nationwide to create a laboratory and technology that will allow us to work more closely with the FDA and to develop an investigational new drug licensing for research and development that will allow us to do some of these procedures currently being done outside the US borders. However, at present time we are limited to some basic surgical transplantation technology that has been discussed in the context of this article. When you extract tissues such as that or bone marrow and centrifuge these cells you actually obtain a tissue “complex” which is a mixture mesenchymal stem cells and a host of regulatory cells. It is the complex mixture of the cells that is responsible for the therapeutic effect in orthopedic application.

There is rapidly emerging technology that involves taking your own stem cells and placing them in culture and expanding specific cells in the mixture. There are methods to take mesenchymal stem cells and placing them in culture and expanding them and even manipulating the cells to express specific lineage such as cartilage, muscle, etc. Imagine being able to have one cell harvesting procedure and placing your cells in a “cell banking” institution where your cells can be cultured, expanded, and you can come in periodically to have “withdrawal” of stem cells that have been expanded tissue numbers and given back to you periodically for regenerative therapy. This technology exists but not the United States. In the US we fall under FDA regulation involving “minimal manipulation rule” where we are unable to take a patient’s cell mixtures and expand and manipulate the cells for specific lineage, etc. What we are able to do in the US is simply a bedside surgical procedure of taking cells from one part of your body and doing a surgical implantation in another location.

These are same-day procedures involve cell harvesting either from bone marrow, fat or both followed by centrifuging cells to concentrate a cell mixture or cell complexes and re-injecting them for therapeutic application. For example, we take bone marrow blood and centrifuge the cells to convince a cell mixture that has potential regenerative capabilities and inject those cells into another location such as a healing bone or joint. That is a surgical procedure that we are able to do in the US. We are not able to take that same bone marrow cell and culture the cells and expand the cell numbers. This is why the US is falling behind rapidly in stem cell therapy.

There are certain diseases that would be best managed by huge numbers of stem cells which would have better therapeutic potential than simply doing a tissue transplantation that we do in the US. Fortunately our focus in this practice is orthopedic application of stem cell and regenerative cell therapies. The same day, bedside procedures that do not involve manipulating your cells, culture rating and expanding the cells are not typically required for orthopedic conditions. There are more complex procedures available outside the US but this is typically not necessary in most conditions.

**WE WILL CURRENT MODERATE TECHNIQUES OF ADIPOSE DERIVED STEM CELL AND BONE MARROW DERIVED STEM CELL THERAPIES WORK FOR MY HIP ARTHRITIS? NOW FOR THE "BAD NEWS"...** Even with moderate advances in stem cell and regenerative therapy technology it does not always work!

We are now living in exciting times where we have the current regenerative medicine technologies that we have today. The majority of patients that we treat seem to have improved pain, disability and function even in more severe degenerative disease. However, when comparing hip and knee outcomes the knee tends to be somewhat better.

Treatment of hip disorders are challenging and required advanced knowledge, understanding and techniques. Treatment of osteoarthritis of the hip with regenerative techniques including stem cell therapy offers more hope but tends to have to be managed more diligently. Sometimes depending on the type of hip condition more than one treatment is necessary or different types of treatment are necessary such as combining stem cell with other strategies.

The key concepts with regard to use of modern regenerative therapies including autologous stem cell therapy is that this is a means to provide a disease modifying therapy. There are a few treatment methods that can slow disease progression, reduce inflammation and pain more effectively than current stem cell technology. Although we have used regenerative injection therapies for 25 or more years we have not been able to make changes that could be monitored on MRI. We are certainly entering a new era of management of orthopedic pathology using current modern methods that are emerging today. We have certainly seen this to be true in the knee.

We desperately need research data and long-term outcome studies for the same methods in the hip. The critical step is to reduce risk factors, decrease biomechanical stress on the hip as we have previously described and to utilize regenerative strategies that can accomplish our therapeutic goals. Since we are utilizing a concept of disease modification these treatments may need to be repeated periodically. The question is going to be, how often? This is highly variable depending on the patient's individual characteristics, anatomy, and severity of disease. Some patients can do well for several years. This strategy may also be to delay what may be an ultimate total hip replacement. Many individuals need to "by some time" and maintain function and reduce pain until it is convenient or they have the ability to undergo a total hip arthroplasty in the future.

#### **WHAT TO EXPECT FROM A STEM CELL THERAPY PROCEDURE:**

I have written a detailed article on what to expect from stem cell procedure which also discusses risks and benefits. That document is available upon request and is always sent to all of our patients considering stem cell therapy. In short we utilize a lipoaspirate procedure to obtain fat cells or a special bone marrow aspiration procedure to obtain bone marrow cells. We described this in more detail in our article on this website entitled "beyond stem cell therapy". And we go through a great deal of detail in our article "what to expect from the stem cell therapy procedure" which will be submitted upon request.

#### **IN SUMMARY:**

Current methods of stem cell therapies utilized today represent great progress with the treatment of osteoarthritic disease of the knee. In my 30 years of practice I have never encountered a

therapeutic intervention that has greater promise and empirically provides the outcome that I have been able to obtain clinically. I have used countless injection procedures and techniques including prolotherapy, platelet rich plasma injection, and a host of complementary and alternative medicines including prolozone all of which does not match the outcome of adipose and bone marrow derived stem cell therapies. We are heavily involved in documenting and researching clinical outcomes utilizing this method of treatment and in the development of new technology for the future.

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