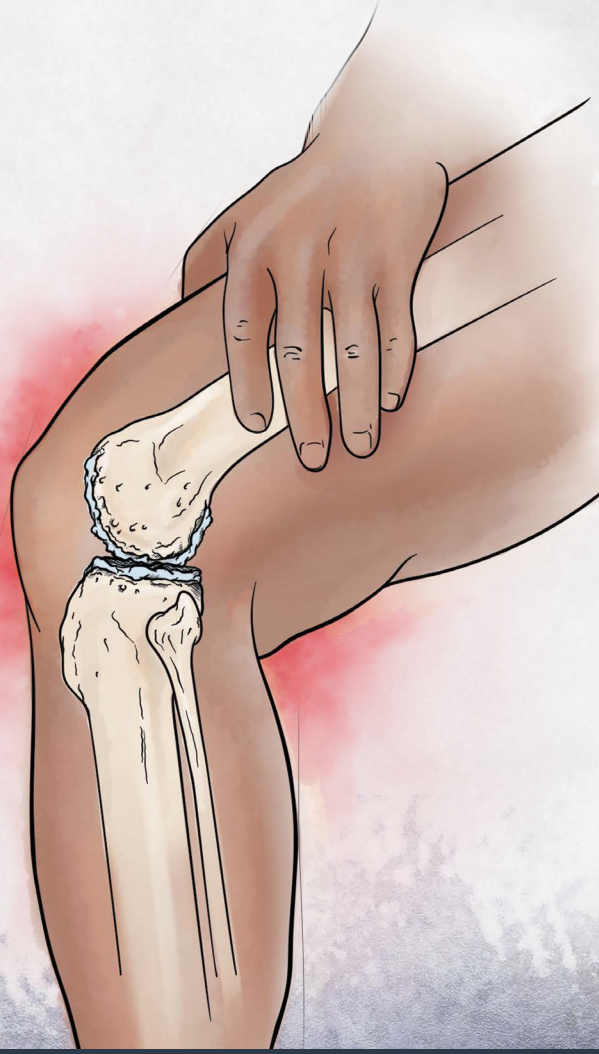
ADVANCED TREATMENT GUIDES

Curing Arthritis with Stem Cells



The truth about knee replacements, joint treatment, and options for improving quality of life.

DR. CHARLES MOK

CURING ARTHRITIS WITH STEM CELLS

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Advanced Treatment Guides

Dr. Charles Mok

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Dr. Mok's Stem Cell Video Series

This eBook is equip with videos throughout the chapters to further explain the concepts and benefits of stem cells.

Click the video below to be directed to the whole YouTube playlist of videos.

Innovative Stem Cell Therapy for the Knee

Dr. Charles Mok explains the process of reversing arthritis through stem cell therapy. ***Click to watch the video.***

INTRODUCTION

Stem cells are primitive cells in your body that are lying dormant that have the ability to differentiate or turn. into various cell types. In some places in the body (i.e., skin, digestive tract, and blood), stem cells are routinely called upon to regularly replace damaged cells. Other stem cells (i.e., certain circumstances, such as in response to a direct injury. As we've developed a better understanding of stem cells, we have learned how to access stem cells that are lying dormant in organs that do not have a need for them, separate the cells from the existing tissue, and then transplant them into damaged tissue in a different part of the body.

The most common use for stem cells had been for people with blood disorders. First, doctors would obtain stem cells from their bone marrow and then store them. While the stem cells were stored outside of the patient's body, the patient would be given a drug that would suppress the abnormal cells. After a period of recovery, the original stem cells or cells from a healthy donor would be transplanted back into the patient. This is how some types of leukemia were treated.

"...access stem those in the pancreas, heart, cells that are lying and lungs) don't turn over dormant in organs... quite as often— they are separate the cells... only called upon under then transplant them into damaged tissue in a different part of the body..."

Scientists started looking at using stem cells to treat arthritis. To do this, they turned to what they were comfortable with, which was stem cells removed from bone marrow. Researchers would numb a person's hip, drill a little hole in the bone, remove some stem cells, and inject them into the arthritic joint. The initial results were promising—people's joints improved even when they had severe degenerative joint disease. As time went on, scientists started discovering that the amount of bone marrow stem cells needed to treat arthritis was quite substantial and that it was a difficult procedure and fairly painful for the patient.

> "...any kind of fat, whether belly fat, arm fat, or neck fat, has a rich supply of stem cells."

More recently, we discovered something we knew nothing about years ago, which is that fat tissue—any kind of fat, whether belly fat, arm fat, or neck fat—has a rich supply of stem cells.

This led to a new opportunity for us. We typically have an abundant amount of fat, particularly people with arthritis (who tend to be a little heavier). Also, we've discovered that stem cells in the fat tissue are pretty much identical to the stem cells in the bone marrow…yet they are about 500 times more abundant in fat tissue. Let's think about that again: there are about 500 times more stem cells in a teaspoon of fat than there are in a teaspoon of bone marrow. And it's easy to extract stem cells from fat using a minor liposuction procedure: the removal can be done with local anesthesia, and the procedure has virtually no recovery time or discomfort for the patient.

When talking about stem cells, I will use the term "stem cells" interchangeably with "mesenchymal stem cells" and "stromal vascular fraction." Stromal vascular fraction (SVF) is the stem cell makeup that comes from fat. It is not just mesenchymal stem cells there are also other cells called preadipocytes (or "baby" fat cells), mesenchymal stem cells, endothelial progenitor cells, T cells, B cells, mast cells, and macrophages. This is the makeup of SVF. Even though we think of mesenchymal stem cells as a primary source or cell, we don't separate the SVF out of the mesenchymal stem cells—the other cells within the SVF aid the mesenchymal stem cells and their functions, so we use them all together.

> "...it's easy to extract stem cells from fat using a minor liposuction procedure... and has virtually no recovery time..."

At the time of this writing, there is more research and practice using human umbilical stem cells which are obtained right after a healthy birth. Umbilical stem cells are not to be confused with embryonic stem cells which are derived from fetuses.

Umbilical stem cells are collected after a healthy baby is delivered. Instead of discarding the stem cells from the mother's umbilical chord, they are kept. Umbilical stem cells are very promising as there is an abundant and renewable supply. Umbilical stem cells are young and have yet to undergo senescence (something we will talk about later). They are just as safe and effective as other forms of stem cells.

Other forms of stem cell therapy that are promising are stem cells derived from the placenta, as well as stem cells obtained from ammonitic fluid. Both ammonitic and umbilical stem cells are obtained from labs that analyze the blood (from a healthy umbilical chord or ammonitic fluid) and check for any known infectious diseases.

Later, we'll discuss how stem cells work and why this field is ever changing. We'll even talk about "exosomes" which are little secretions from stem cells that may be just as effective as stem cells, themselves. As a bonus we'll also touch on why scientists are racing to find peptide molecules that can signal tissues to repair in the way that stem cells do.

The History of Stem Cell Therapy

Click to watch the video.

SECTION 1

HOW IT WORKS

An important question would be: "How often does stem cell therapy for arthritis work?"

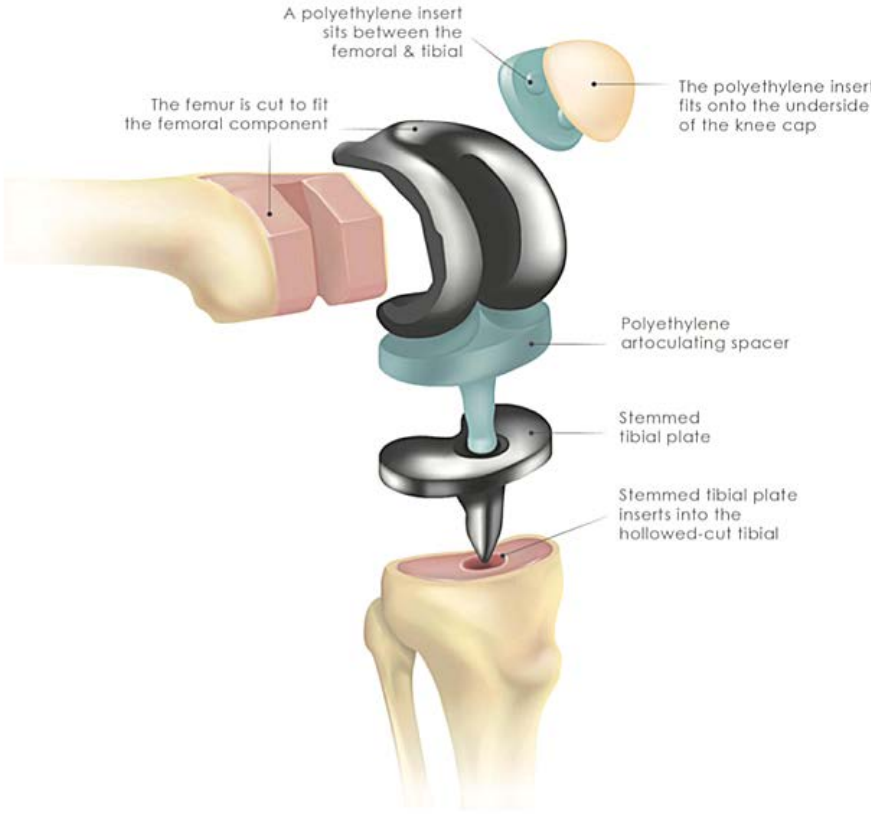
A larger study in the current literature reviewed the results of 1,128 patients receiving stem cells (or SVF) on 1,856 joints. The joints were mainly hips and knees. Because there were 1,856 injections on 1,120 patients, some people had more than one injection. They were followed for one year to six years. This is a pretty long period for follow-up in a clinical study—six years is a substantial amount of time. Most of the studies I've seen looked at patients over a three- to six-month period. (The reason for this is that when a study is being done, usually we're looking at early endpoints to demonstrate clinical effectiveness, whereas a long-term study is done to assess long-term durability.)

In this study, researchers used adipose (i.e., fat-derived) stem cells. The patients were all candidates for total joint replacement, in other words, they were "bone-on-bone" and had severe arthritis, making them candidates for surgery. The researchers found slow and steady improvement in

> "What the researchers found was that at the one-year mark, over 90% of patients had better than a 50% improvement of their symptoms."

the patients when they assessed them at three, six, and twelve months. At each point, the patients got a little bit better. What the researchers found was that at the one-year mark, over 90% of patients had better than a 50% improvement of their symptoms. This means that 90% of the patients—and again, there were about 1,100 of them—would no longer be eligible for knee replacement because they were over 50% improved. This is substantial evidence for us to consider stem cell therapy as first-line therapy.

One thing the researchers noticed in this paper (since this was



COMPONENTS OF KNEE REPLACEMENT SURGERY

really the largest patient cohort and the patients were followed for the longest amount of time) was that compared to people of more normal weight, people who were heavy went a longer amount of time before they saw an improvement of their symptoms. However, both groups had the same eventual outcomes. It didn't matter whether they were heavier or thinner, young or old—everybody saw improvement. And again, these were all candidates for total joint replacement.

"...stem cell treatment does not involve the morbidity or complications that are associated with total joint replacement..."

Remember that total joint replacement is associated with the persistence of significant symptoms in about 1 out of 5 people, and in this case, 9 out of 10 people had significantly reduced symptoms. When compared to joint replacement, stem cell treatment is obviously a much better option. And stem cell treatment does not involve the morbidity or complications associated with total joint replacement—when total joint replacement surgeries are done, there is a substantial risk of serious consequences. About 2% of people who undergo total joint replacement have complications such as blood clots, heart attacks, strokes, infection, and even death.

Another study published in April 2017 did what's called a meta-analysis. The prior study with about 1,100 patients was one series of studies done at a variety of clinics. A meta-analysis is a study in which researchers look at multiple different clinical studies and pool them together to remove any potential bias. This meta-analysis was called "Clinical Efficacy and Safety of Mesenchymal

Stem Cell Transplantation for Osteoarthritis Treatment: A Meta-Analysis." To carry out the meta-analysis, researchers found 11 clinical papers with similar characteristics. In general, patients were followed for around 24 months and they all had about the same degree of improvement. Initially with stem cell therapy, there is a strong anti-inflammatory effect that happens at the injection site. As this effect wanes, the joints will become sore again, but over the next couple of months, patients improve and continue to improve for about a year or two. (We'll talk about the overall durability or duration of the results in a bit.)

> "...the patients were continued to improve followed for an throughout the 24-month average of 24 months, period. This is something we and they got better see in our clinical practice every month through right after we do the stem the 24-month period."

The meta-analysis shows us there isn't just one individual study showing improvements—studies of mesenchymal stem cell treatments have consistently shown improvements in disability, pain, or discomfort in people with degenerative joint disease. Another meta-analysis looked at about 117 clinical studies and narrowed the studies down to fewer than 20 that were very similar. Again, researchers found the same results: the patients were followed for an average of 24 months, and they got better every month through the 24-month period. The researchers also noted that the people who were early responders and who had substantial improvements early

on did not lose those improvements over the 24 months.

"...about 20% of people are left with significant symptoms after joint replacement, there's a substantial risk of major complications..."

So, the next question is: "How long does it last?" Knee replacements are designed to last for several years but it's only a matter of time before it needs to be replaced again, which is anywhere from 10 to 20 years. This is why people who are younger typically try to avoid replacing their knee for as long as possible—they don't want to have more than a couple of knee surgeries in their lifetime.

This leads to tolerating pain and discomfort because while the treatment may be better than the disease, it isn't a whole lot better. Again, about 20% of people are left with significant symptoms after joint replacement, there's a substantial risk of major complications, and these surgeries certainly mean substantial downtime. Who wants to go through surgery?

Back to the question about how long stem cell treatments last. First, somebody with arthritis has it for a reason. They were walking on the joint hard, or they were running, or they were partaking in activities that contributed to the arthritis forming. These activities may continue, in which case the joints will continue to be damaged.

To set this up, I want to talk about what's actually happening in the joint. Some studies show there's growth of cartilage, and I'll

talk about that little bit later, but what is actually happening on a biological level? To answer this, scientists looked at animal models, where they could inject stem cells and look at what happened to the cartilage inside the joint. (We can't do this in people, of course.) In a study done with rabbits, scientists isolated the fat-derived stem cells and injected them into the joint.

Now, doing this stimulates the growth of new cartilage. What happens—or what we assume happens—is that with arthritis, even when it's "bone-on-bone," there is cartilage left behind still doing what we call paracrine signaling. The paracrine signaling is a juice that damaged cells give off to communicate with other cells, telling them to replace the damaged ones. Here's how that's supposed to happen. Inside your joint, you've got stem cells and cartilage, and as you're wearing your joint down, you're killing chondrocytes, which are the cartilage cells. When these cells become damaged and they die, they give off paracrine juice to signal a stem cell sitting right next to them to turn into a cartilage cell. Over time, from repeated damage to the cartilage, you basically run out of cartilage stem cells, causing the cartilage to wear down so much that eventually, you get down to bone-on-bone. This causes pain. This is a signal to get off your feet because your damaged joints are no longer working

In this animal study, however, the researchers showed something else, something we never suspected. We already knew that when we put stem cells inside the joint, regardless if the cells are derived from bone marrow or fat, they can turn into cartilage, widening the joint space so the pain caused by bone-on-bone can go away. But what the researchers found was that when stem cells were injected into the joint, the stem cells themselves

gave off paracrine signals to decrease inflammation, which slowed down damage to the cartilage. This was a pretty amazing discovery. Injecting stem cells into the joint created protection and stimulated the chondrocytes—the cartilage cells—to grow and improve the matrix, which is the underlying structure of the cartilage itself. We had been presuming that the stem cells simply replaced the damaged cartilage cells, but they do more than that: stem cells stimulate healing inside the joint, and they are protective against further cell death. Stem cells heal the joint. Again, this was an animal study, but it gives us good insight on what is likely happening.

Another study published in 2017 followed seven patients for seven years after they had had stem cell injections into the knee joint. The researchers found that patients had substantial improvement of their symptoms fairly rapidly, over roughly three to six months. They continued to have the same improvement over the entire seven-year period.

At this point, we don't really know how long stem cell treatments will last. In our clinical practice, we've treated patients a second time after six months, a year, two years, but all those cases were people with substantial improvement in pain. They weren't coming back in because their symptoms were coming back, they came back in because they wanted to have even more improvement. They were so surprised at how good their improvement was that they came back for more.

A friend from Missouri, Dr. Colin E. Bailey, had shattered his knee back in 1998 in a motorcycle accident. He was told he could never run again. As an active triathlete, this was devastating for

> "...in healthcare, we're just managing chronic illnesses, whereas stem cell therapy regenerates our bodies back to where they were before."

him. Over the years, he ran intermittently and the pain and swelling in his knee became debilitating. He asked me to do stem cell treatments on his knee. Once we did the procedure, he saw improvement within a month or two. He called me a few months later and said, "I should have had you do both knees—I didn't even know my right knee hurt until the left one felt so great! My knee is not perfect, but it is at least 80% better and continues to improve."

This is remarkable. We get used to having symptoms and we think that's just our baseline or that we're "getting old," but in reality, this is what we deal with when we're talking

12 regenerative medicine. Typically, in healthcare, we're managing disease and managing chronic illnesses, whereas stem cell therapy regenerates our bodies back to where they were before.

SECTION 2

THE TELLING TRUTH: MRI

When stem cells were first introduced as a treatment for arthritis, we initially saw that the patient's pain improved. However, critics of the procedure criticized the mechanism. The assumption was that stem cells decrease inflammation and probably build some cartilage. So the first questions are: "What is actually happening? Is there just an anti-inflammatory response, or are the stem cells actually fixing and regenerating the knee?"

As early as 2008, in a study published in Pain Physician Journal, researchers conducted a study evaluating the effect of stem cells on knee cartilage. In the study, researchers found that three months after injecting stem cells into the knee joint, MRIs showed that the cartilage—which is the lubricating pad of the knee joint—had increased by about 25%. This is remarkable. Until this time, nothing short of knee replacement surgery increased joint space by that much.

There are other treatments commonly used to lubricate the joint or to decrease inflammation, such as steroids or hyaluronic acid. These reduce pain, but these treatments only last a short amount of time and are

"...steroids or hyaluronic acid... reduce pain, but only last a short amount of time and are not regenerative."

absolutely not regenerative. By decreasing inflammation, steroids may also wear the joints out faster, and the lubrication effects of the hyaluronic acid give no added benefits.

What about people with "bone-on-bone" arthritic pain? A study published in 2016 evaluated the effect of stem cells injected into the knee of a 47-year-old female with severe single-knee arthritis. Hers was a case of bone-on-bone: her knee showed a big defect, with close to no cartilage covering part of the bone and an absolute absence of cartilage on another part. After stem cells had been injected, the MRI showed that cartilage had grown where there previously was none, where it had been completely worn away. The takeaway here? There's no evidence that the severity of the arthritis will predict success or failure —numerous studies have shown that almost all people respond substantially to stem cell therapy.

"After stem cells had been injected, the MRI showed that cartilage had grown where there previously was none..."

As we move forward and add more techniques to our treatments, change the techniques we're using, and include additional growth factors, the success rates are getting higher and higher. A case report published in 2017 evaluated a young man with a condition called osteochondritis dissecans, which is an inflammation of the joints. In his case, it was his knee. (The defect in his knee was large—about the size of a postage stamp.) This

individual had undergone seven operations to try to repair his damaged knee. He continued to have pain for several years, and after several operations, his doctors declared that he was a complete surgical failure and decided to use stem cells to treat him instead. They did a single injection of stem cells. The MRI showed that cartilage then grew in this area of his knee where he had had the osteochondritis dissecans cartilage defect. His doctors repeated the stem cell treatment six months later to get additional benefits. Basically, this was a case where the individual had had seven failed surgeries and then was cured with just two stem cell treatments. That is a dramatic difference, especially compared to (unsuccessfully) operating, with all of the morbidity risks and downtime that surgery entails.

> "...numerous studies have shown that almost all people respond substantially to stem cell therapy."

We've discussed that MRIs show that patients regrow their cartilage and that the regrowth starts as early as two or three months after treatment, with studies following people for as long as six months. We also know that people have improved symptoms, typically for several years after having received injections, and that they continue to improve for the first six months to a year. We also know this improvement stays pretty steady for a long period.

A study published in 2015 looked at a two-year follow-up study of stem cells treatments in the knees. This study involved 24 patients. They each had one knee treated with stem cells, and they had pre-procedure MRIs and two-year follow-up MRIs. This study confirmed that the changes in the knee—the improvement of the joint space and the improvement of the thickness of the cartilage—persisted for two years. Again, that's remarkable when compared to any of the currently available procedures.

Remember that a knee replacement has a time window—eventually, it will fail. And the current available non-stem-cell injections are only basically putting Band-Aids on the problem. With stem cells, though, it's been shown that for at least two years following the procedure, there is definite cartilage growth and maintenance, and then based on clinical studies, we also know that the improvement lasts for at least 5 to 7 years. It may last even longer—this is yet to be known. Another common question is whether we should be treating people with the most severe forms of arthritis. Maybe the patients who undergo stem cell treatment are not quite as badly off and they would consider stem cell treatments, whereas patients with more severe degeneration may not benefit from stem cell treatments. As I mentioned before, however, there was a study with about 1,100 people who were all candidates for total knee replacements. Let's look at the people with the most severe arthritis.

A paper was published in 2016 titled "Adipose Mesenchymal Stromal Cell-Based Therapy for Severe Osteoarthritis of the Knee: A Phase 1 Dose Escalation Trial." In this study, the researchers studied

people with the most severe arthritis as defined by a scale called

the Kellgren & Lawrence scale. In this study, 80% of the patients were grade 4, which is the most severe arthritis. On a grade 4 patient's X-ray, it looks like the upper bone is impacted into the bone below. This causes severe pain. The patients in this study were treated with fat-derived stem cells. Fat is much richer in stem cells than bone marrow is, so you get a much higher yield from fat. Here, researchers used varying numbers of stem cells, injecting between 2 to 50 million cells into the joint.

"Fat is much richer in stem cells than bone marrow is, so you get a much higher yield from fat."

When reviewing the results from using bone marrow-derived stem cells, there was a correlation between how many stem cells were used and how much benefit the patients saw. When fat-derived cells were used, however, the patients—regardless of whether they received low, medium, or high amounts of cells—all got about the same benefit: at about one week, their pain was substantially better (specifically, about 50% better), and they continued to improve during the study. Again, these were patients with severe osteoarthritis, which is the worst of the worst. They still had substantial improvement in pain.

When stem cell therapy is performed using umbilical stem cells, results appear to be as good or better than other sources of stem cells and may last longer.

> "...at about one week, their pain was substantially better (specifically, about 50% better), and they continued to improve..."

The source for stem cells, although there is evidence of subtle differences, is not critical. They all seem to be effective but all come with pros and cons. The good thing is that all forms of stem cell therapy are being actively studied. You and your health care provider will choose a source of stem cells based on what is practical and most appropriate for you. The decision will also be made with the most current evidence based medicine in mind. Just remember that stem cell therapy is constantly evolving as more studies are performed around the world.

SECTION 3

PRP, HANDS AND OTHER JOINTS

Another treatment that's been considered for knee pain has been platelet-rich plasma or PRP, which has been shown to be helpful in orthopedic medicine as a healing mechanism. Platelets are the cells in your blood that promote healing when you're wounded. If you cut yourself, for example, the platelets are activated. They spit out all kinds of growth factors that allow the blood to coagulate; after that, they call for specialized cells to come in and repair the tissue, contract the edges of the wound, and grow new skin that will create a scar. The scar might look unsightly because your body may have reacted very fast and somewhat randomly, but then again, sometimes, the healing process goes more smoothly and the scar looks acceptable. This is because the collagen was laid down and the wound was tightened in a very speedy manner to protect you from bleeding and infection.

Maximizing Stem Cell Results

Click to watch the video.

Knowing how effective platelets are for healing led us to start using platelets to facilitate wound care. Let's say somebody has a surgical scar or surgical incision. If we put additional platelets in the wound when we close it, we actually get a better wound. If someone has a tendon injury, you can inject platelets into the tendon, and it will typically heal.

I had personal experience with this. I injured my right rotator cuff (the subscapularis tendon) about 10 years ago. It kept hurting. I initially injured it when I was playing with my kids in the pool and I was throwing them up in the air. After that, every time I put my arm through a similar action, I would have some discomfort. I had a few steroid injections; they would settle down my arm for a year or so. An MRI scan showed that the subscapularis tendon was about 90% torn. I'd do exercises to try to improve it, but it was a really chronic injury, and it was hard for me to do things such as liposuction and other tasks at work.

I wound up being scheduled to have open-shoulder surgery because the surgery was going to be sufficiently complicated

that the doctors would not be able to do surgery through a laparoscope. I was a little bit concerned about this because they would have to cut my biceps tendon and I'd have a big scar on my arm, so I started searching alternatives. Platelet-rich plasma was just starting to be used in 2009, although it hadn't yet been explored as a way of treating athletes with tendon injuries. I bought a platelet-rich plasma-separating machine and had my ultrasound tech learn how do shoulder ultrasounds. Then I collected my own platelets and asked a friend, Dr. Jim Kehoe, DO, to inject the platelets under ultrasound guidance. He injected

them right into the tendon—you could see the platelets going into the tendon.

I had a rapid improvement of symptoms, and my arm strength got a little bit better. I repeated the PRP treatment two months later, even though it seemed pretty much healed. That's the protocol I had read about in the studies, that people were having treatments done twice. I can tell you this: I did the treatments in 2011, and my shoulder has been normal ever since. Completely normal, whereas before, I had experienced significant physical limitations.

I later ran into one of the orthopedic doctors originally supposed to do my shoulder surgery. (He was a shoulder expert.) I told him what had happened. I was pretty excited—I thought he'd want to jump on board and start doing this procedure himself. I was surprised that he had a very negative response to it. He said that it probably wouldn't last, probably wouldn't work very well, and probably wouldn't work for everybody. This is a typical pattern I see when we discover new things: for every new discovery in healthcare, there are a thousand self-appointed guardians of the past. People have a tendency and a rather natural motivation to maintain the status quo.

At any rate, some doctors did research on adding platelet-rich plasma to stem cells to see if it might benefit overall arthritis recovery. Studies were initially done that just evaluated adding platelet-rich plasma to stem cells. Researchers saw good results, but they weren't comparing those results to not using platelet-rich plasma—basically, they would combine the stem cell and PRP injections and got results that were better than they had

expected. These were preliminary studies.

In a study in the Journal of Pain Research done in Australia in 2015, researchers evaluated the use of stem cells along with PRP. They gave several patients a questionnaire regarding their ability to walk (in terms of pain and discomfort they experienced) and treated the patients with a combination of stem cells and PRP. They found that the patients saw remarkable improvement in their symptoms. We talked earlier about the study done with over 1,100 patients that showed that about 90% of the patients saw an improvement of over 50%. In this Australian study—where the researchers utilized platelets along with stem cells—all patients had substantial improvements, seeing an almost 100% improvement with this combination. This was remarkable.

A study published in 2014 compared using fat-derived stem cells with platelet-rich plasma versus using fat-derived stem cells without platelet-rich plasma. The researchers specifically found that using PRP led to increased cell proliferation compared to using stem cells alone. The stem cells became more active or more energized in the presence of PRP. They also saw there was a more positive development for growing cartilage versus growing bone. Arthritis might already cause a bone-on-bone environment—obviously, it's better for patients to grow more cartilage, not more bone. Adding PRP to stem cells led to more proliferation of cartilage and a very beneficial improvement. This seems why we see much better results when we combine PRP with stem cells.

Another traditional treatment for arthritis is hyaluronic acid. Hyaluronic acid is a naturally occurring sugar in our body that acts

as a lubricant for the building structures of different tissues. An initial question would be: "Do stem cells work any better than hyaluronic acid?" We already know the answer—hyaluronic acid does little — but here's a study comparing the two treatments. In 2016, researchers evaluated the joint space after treating patients with stem cells and treating patients with hyaluronic acid. They used X-rays and physical examinations of patients' symptoms. The results? After stem cell treatment, the X-rays showed an improvement of the joint space, but with hyaluronic acid, there was no difference.

"People experience some degree of improvement of their symptoms and may put off having knee surgery, but hyaluronic acid injections do not prevent eventual surgery."

For years, doctors have been injecting hyaluronic acid solutions (it's a thick liquid) into the knee to relieve knee pain. Typically, this is done about three times, a month or two apart. People experience some degree of improvement in their symptoms and may put off having knee surgery, but hyaluronic acid injections do not prevent eventual surgery. Scientists evaluated whether or not adding hyaluronic acid to stem cells with or without PRP would improve outcomes.

A study published in 2016 evaluated adding hyaluronic acid to stem cells and how it behaved inside of the joint. Researchers found that adding hyaluronic acid to the stem cells causes stem cells to adhere better to the desired tissues. With PRP, we note

increased proliferation of stem cells; with adding hyaluronic acid, we see that the stem cells will be directed to the tissues we desire instead of just floating around in the joint. So to see what would happen if both were used (with hyaluronic acid stimulating the stem cells to stick to the proper surfaces and platelet-rich plasma increasing cell proliferation), a study was done in 2016 to evaluate the clinical response to the combination of fat-derived stem cells, PRP, and hyaluronic acid. In this study, researchers gave patients this combination of injections and followed them for several months.

They found remarkable improvements in pain starting as soon as just a couple weeks after treatment; these improvements continued during the study. Combining PRP, hyaluronic acid, and adipose-derived stem cells showed continuous improvement and are steering us to better, more consistent results.

Another study—this one published in 2017—evaluated the outcomes of using hyaluronic acid combined with stem cells. Researchers followed patients by tracking both their symptoms and their progress via MRIs. They found that at the seven-year follow-up, patients continued to have improvement of symptoms and improved MRIs. When researchers looked inside the knee with an arthroscope, they saw development of new cartilage.

"When researchers looked inside the knee with an arthroscope, they saw development of new cartilage."

This answered a lingering question. We had seen improvements in MRI scans and X-rays, but were

we seeing actual new cartilage or just some other tissue? The results proved that what we were seeing was definitely cartilage formation—the knees looked like normal knees. It's remarkable that we have seven-year evidence showing restoration and maintenance of normal cartilage after having injecting fat-derived stem cells combined with other growth factors.

Most of the studies done with stem cells have focused on the knee. That's because it's very easy to do studies on the knee—there are well-established guidelines for rating pain and differentiating the amount of arthritis by using X-rays. There's also a correlation between X-ray and MRI findings and physical examination findings, plus arthritic knee pain is a very common problem in the United States (compared to other places in the body where people experience arthritic pain). But arthritis occurs everywhere. Other papers have looked at using stem cells in the hips, ankles, and shoulders, and they've found similar results: long-term studies show that hip, shoulder, and ankle arthritis respond to stem cells as knee arthritis does.

"Long-term studies show that hip, shoulder, and ankle arthritis respond to stem cells in the same way knee arthritis does."

We've treated multiple joints. My mother had her thumb MCP joint injected (that's the joint between your thumb and your hand). She had arthritis and was wearing a splint—it was really causing her some difficulties. We did two injections right into that joint, and now she's out of the splint. She still has a little bit of discomfort at

times, but it's about 90% improved. This is remarkable because at that time, standard treatments would have been just living with it and wearing a splint so she couldn't move her thumb or putting in an artificial joint, and she's not interested in having surgery at her age.

Stem cells for joint arthritis is really an emerging treatment. As of right now, insurance companies don't cover it…even though we're spending about $11 billion a year nationally on total joint replacement. It's estimated that the cost to the healthcare system for somebody with arthritis without joint replacement is about $20,000 to $30,000 because of chronically prescribing various medications for patients and administering different injections.

Studies have shown that the cost-effectiveness of replacing a joint is realistic—if a joint is replaced, the cost goes up to about $70,000 per individual, and the new joint is good for probably about 10 years, maybe longer.

Even with the high cost of arthritis care, insurance won't pay for stem cell treatments yet, mostly because the procedure is too new. It usually takes insurance companies 20 to 30 years to adopt paying for something that represents a major paradigm shift. Other interests such as medical device manufacturers, hospital operating rooms and surgeons who specialize in joint surgery, want to preserve the status quo.

"...the cost of stem cell treatment is a fraction of the current patient care cost..."

Another issue for insurance companies would be to

analyze whether many more people would seek treatment if the insurers covered a simple, nonsurgical treatment. Right now, they are paying around $70,000 for joint replacements and about $30,000 for lifelong patient maintenance with medications and injections. In reality, the cost of stem cell treatment is a fraction of the patient care cost, and we know from studies that have been done on stem cell treatments that they last at least seven years. If we compare stem cell treatments to joint replacements or just maintenance with prescriptions and injections, it is an absolute home-run to treat people with stem cells. Right now, however, you have to pay for it yourself, but you save a lot of disability, discomfort, injections, surgery, and downtime. Nothing favors using the current non-stem-cell medical therapies other than "This is what we've always done."

"The safety concerns and adverse effects involved with stem cell treatments, are very few."

The safety concerns and adverse effects involved with stem cell treatments, are very few . Large scale studies on safety have reported some minor cases of injection related complications such as infections, bruising and swelling.

Using Fat Derived Stem Cells

Dr. Charles Mok discusses how life changing treatment is created using a patients own fat derived stem cells.
Click to watch the video.

SECTION 4

TODAY'S STEM CELLS

The stem cells we are using today are called "human adipose-derived stem cells," meaning we're getting the stem cells from your own fat. Much of the original stem cell research revolved around using cells from bone marrow because these were available and we knew how to use them. When it was discovered that fat is a much richer source of stem cells—(about 500 times more stem cells per teaspoon than bone marrow)—and that fat-derived stem cells work just as well (if not better), the practice of using the latter became obsolete. It's still being done simply because there are FDA-approved kits for using bone marrow-derived stem cells, but they don't work nearly as well. In fact, we don't use stem cells derived from bone marrow at all.

Some people might not have enough fat to use for deriving stem cells. Another option is using what's called "human umbilical derived stem cells." Umbilical stem cells have the advantage of being radially available, easier to perform in an office setting, and are as effective if not more effective than fat derived stem cells.

There is also something called "expanded stem cells." This is where you take a small number of stem cells from somewhere in your body (such as your bone marrow) and then have them grown and multiplied in a lab. Once there are enough of them, the lab sends the stem cells back to your physician, and you have them injected. Right now, this procedure is in a state of regulatory clarification. There are, however, multiple drug manufacturers

looking to capitalize on this huge potential market, and we'll see something along these lines in the future. The scenario may look a bit like this: your doctor numbs a patch of skin, takes a little skin biopsy, and sends it to a lab. The lab separates the substrates out of the stem cells and expands them by growing them, then sends back a vial of your own stem cells, at which point they're injected into your joint. We aren't there yet, but it'll happen.

What is Senescence?

The most fundamental change in the way we understand stem cell therapy has come from the understanding of "senescence". As we discussed earlier, your body's cells are constantly being damaged and replaced with local stem cells. But as the years go by, some of these cells have minor damage that progresses into a mutation or near mutation. This could lead to the growth of abnormal tissue like cancer. These damaged cells are programmed to go into senescence, which is a zombie-like state (almost dead). When many of these senescent stem cells are in the tissue, they signal other healthy stem cells to do nothing, or signal normal tissues not to go through regeneration. Our body uses the process of senescence to protect us from cancer, but eventually leads to our organs or tissues wearing out as we age.

Understanding the healthy vs. senescent state of our cells is key to unlocking discoveries in stem cell therapy. We used to think that stem cells would implant and repair, now we know that they send cellular signals, and either overpower the senescent signaling for the tissues to be passive, or signal other cells to take over. We can recreate this process by injecting stem cells that use exosomes (tiny droplets of cellular signals) to repair tissues, exosomes by themselves, or in the future, just using targeted signaling peptides.

Allure's Stem Cell Treatment

Currently, a physician will evaluate you by doing a limited physical exam and looking at your X-rays or MRI reports to determine if you're a candidate for treatment. Most patients we treat in our practice have already had a relationship with a doctor, so they've already had an evaluation of their problem joint. If there's some significant deformity—perhaps the knee is substantially bent; for example—you can expect that the stem cells won't last very long, but it is still reasonable to consider treatment. Usually the knee is a little bit swollen and painful, the X-ray shows degeneration, and the MRI shows some lack of cartilage.

To obtain fat derived stem cells:
The process involves first numbing your skin with a technique called "tumescent anesthesia." We take lidocaine (a numbing agent) and epinephrine (which causes the blood vessels to shrink) and bicarbonate (which minimizes the solution sting) and inject this underneath your skin. It's not completely painless, but it's pretty close to painless. That takes about 10 minutes. The selected site may include your waist or your back or anywhere you want to get rid of fat. (Stem cells are equally abundant in all fat, so we find a place where you have fat you want to get rid of.) This is not the same as doing liposuction—we're not contouring your body; we're just finding an area where we can harvest some cells. Still, we use a similar technique. After the numbing sets in, a little hole of about a millimeter (about 1/16 of an inch) is made in your skin, and a cannula (a long tube, much thinner than a pencil and with holes at the end) is attached to a syringe. The syringe is drawn back, creating negative pressure. A slow, back-and-forth movement separates the fat cells.

> "Stem cells are equally abundant in all fat, so we find a place where you have fat that you want to get rid of."

The first technique for obtaining adipose-derived stem cells remains the most common, so we will talk about that first; then, we'll talk about something we are doing now that's more modern and gives a better yield.

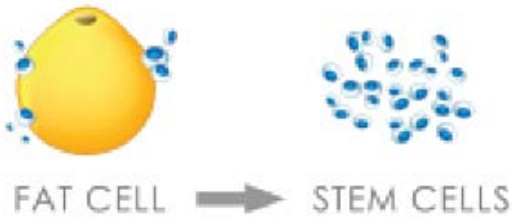
The traditional method for deriving stem cells from fat has been to add an enzyme called collagenase to the fat. Collagenase is an enzyme that breaks up collagen, which is the connective tissue or the building block that holds the fat in place. When you look at fat (if you've ever seen it when you've cut yourself deeply), there are little pearls of fat. That's not fat cells that you see—that's just little pearls of fat. Inside the pearls are lobules of fat, which are collections of fat cells. Inside those are fat cells you really can't see with your naked eye.

Stem cells are very tiny—they're about 10 µm. Fat cells are about 100 µm. The nature of size-to-weight ratios generally means that even if two cells have the same material inside, something with a smaller surface area is heavier. That's because the cell wall is heavier than the stuff that's inside of it. So the stem cells at 10 µm are heavier than the fat cells even though the latter are 10 times as big. The collagenase breaks up all these tissues, but the cell wall stays intact. Then, because it's heavier, it is spun in a centrifuge, causing the stem cells to fall to the bottom.

We take those stem cells and go through a process to wash the

collagenase out. (Collagenase in and of itself would be damaging to the cartilage, so we must remove all of it.) Typically, although two passes generally get all of the collagenase out, three passes are done—it's standard to do three passes to make 100% sure the collagenase is all gone. The stem cells are then transferred to another syringe, and a little bit of saline is added. This is injected into the joint along with PRP or platelet-rich plasma, with or without hyaluronic acid.

More recently, scientists and doctors have worked to make the fat derived stem cell technique much easier, as well as a desire to remove the complicated process of separating the stem cells from the fat. There are two commercially available kits that purify or filter the fat, but do not separate the fat from the stem cells. While this process is less common, it is very promising and seems to work just as well, without of the complexity. Additionally, the FDA has indicated that in fall of 2020, they may not allow office-based enzyme separation of fat and stem cells.



For umbilical, amniotic and placental stem cells, and exosomes:

Right now, these are commercially available from laboratories. I won't go into the

details as to how they are processed, as it depends on the lab. But these are purchased the day of or day before your procedure and come in sterile packs that are frozen and need to be used right away upon thawing.

After the injection, you can resume your normal activities. There is no evidence or suspicion that you should take it easy or rest. It seems that the growth will occur in an active environment and may even benefit from an active environment, so you can go on with your normal activities. There may be some swelling afterward where you had the fat removed or in the areas that were injected, but it's generally not significant. Maybe patients take a Tylenol, but typically they don't take any medications, and only a simple bandage is applied. Most people see improvements right away—maybe immediately, maybe within about a week or so. That fades after a few weeks because the original effect was anti-inflammatory. (The stem cells themselves are very anti-inflammatory.) The next step is an improvement of symptoms, an improvement that is durable. This occurs in as little as a month and continues to improve over about a two-month period. As far as we know from clinical studies and from following patients, this improvement can last at least 5 to 7 years, maybe even longer.

I suspect that one day we will no longer be doing joint replacements (or that we'll only be doing them in severe refractory cases) because stem cells are much safer and more effective. They will save the country billions of dollars over the surgeries we are doing now. It will also save people from having

"After the injection, you can resume your normal activities."

to miss work. Most importantly, it will save the quality of life for many patients. Most people put off doing a knee replacement until they absolutely must, but they've been suffering up to that point, and that suffering is totally unnecessary.

Thank you! I hope you enjoyed reading this.

"...one day we will no longer be doing joint replacements, because stem cells are much safer and more effective."

Dr. Charles Mok

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The understanding of stem cell therapy has taken us on a fascinating journey at Allure Medical.

We've made a commitment to our patients to discover cutting edge treatments that are changing lives.

Stem cells that are lying dormant in the body can be awakened ***by stimulating the growth of new cartilage.*** They are separated from fat that comes from different parts of the body and transplanted into damaged tissue.

This promotes healing at a rapid pace, and drastically reduces the chance of needing more invasive procedures such as ***knee replacement surgery.***

Stem cells for joint arthritis is an emerging treatment. As of right now, insurance companies don't cover it... even though we're spending about $11 billion a year nationally on total joint replacement. The cost of stem cell treatment is a fraction of patient care for more invasive procedures, with less downtime.

In This Booklet, We Cover:

- The success rate of stem cell therapy for arthritis
- Seeing real results and cartilage growth in an MRI
- Using platelet rich plasma to improve joint pain
- What our practice offers as treatment options
- Cost of stem cell vtreatment compared to expensive surgeries
- Safety concerns with stem cells
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