Navigating the Hope and Hype of Regenerative Medicine

Regenerative medicine is the process of creating living, functional tissues to repair or replace tissue or organ function that is lost due to age, disease, damage or congenital defects. Mayo Clinic is careful to give patients a realistic picture of what they can expect from regenerative medicine treatments for orthopedic conditions.

Before patients receive orthobiologics at Mayo Clinic in Jacksonville, Florida, they visit the Center for Regenerative Medicine Consult Service, part of the Mayo Clinic Center for Regenerative Medicine. There they meet with a clinical consultant who has expertise in regenerative medicine and the patients’ specific conditions.

“We explain which orthobiologics we use, what the science shows about them and what outcomes we are seeing. We tell patients to please understand that regenerative medicine treatments aren’t necessarily cures or substitutes for surgery,” says Shane A. Shapiro, M.D., a medical orthopedist and medical director of the Regenerative Medicine Therapeutics Program at Mayo Clinic’s campus in Florida. “When we educate patients, they are better able to make decisions that are right for them and their orthopedic conditions.”

This effort exemplifies Mayo’s commitment to evidence-based care at a time when orthobiologics are aggressively marketed to consumers and health care providers.

“Unfortunately, the field has proliferated in a way that is not always backed up by science,” Dr. Shapiro says. “The excitement around regenerative medicine and stem cells has consumed both the public and even care providers who don’t have the background in molecular or stem cell biology to understand what is real and what is entirely false or misleading about these therapies.”

Patients’ visits to the Regenerative Medicine Consult Service include medical evaluations to determine whether orthobiologics are appropriate. Misinformation about the unapproved stem cell therapy marketplace also can be corrected.

“For some patients this is an eye-opening experience, as they have received inaccurate information from websites and other sources,” Dr. Shapiro says. “Infomercials disguised as educational seminars for the public are widespread. In our meetings with patients, we take care not to overemphasize the medical benefits and also to acknowledge any risks of orthobiologics.”

Orthobiologic therapy at Mayo Clinic

Patients who qualify and opt for orthobiologics are treated in the Regenerative Medicine Suites, a novel, multidisciplinary surgical hybrid procedure facility for cell therapy applications. The suites are equipped for regulatory-compliant cell harvest, application, storage, receiving and quality oversight. Mayo Clinic offers procedures that involve...
the patient’s own cells — from blood, adipose tissue or bone marrow — which are minimally processed and returned to the patient within the same surgical procedure. All clinical trials using orthobiologics are monitored by the FDA.

“Patients may experience relief of pain and improvement in function for up to a year or longer. But most procedures should not be considered a cure,” Dr. Shapiro says. “All would likely need to be repeated over time — with some exceptions, such as procedures in younger patients with tendinopathies, in which cures are certainly possible.” Biologic therapy is also regularly combined with best practices such as activity modification, bracing and physical therapy.

Among the orthobiologics offered at Mayo Clinic is platelet-rich plasma, which uses the patient’s own platelets and growth factors to promote musculoskeletal healing (Figure 1, on page 1). In recent years the protocols for this therapy have been refined and standardized, leading to more consistently positive results.

“We are seeing a significant clinically beneficial effect to using platelet-rich plasma in tendinopathies, as a surgical adjunct to rotator cuff repair and as pain relief for knee arthritis,” Dr. Shapiro says.

Mayo Clinic also offers newer treatments using cells derived from patients’ adipose tissue or bone marrow. Notably, bone marrow aspirate concentrate therapy achieved positive results in a Mayo Clinic study of patients with osteonecrosis of the femoral head. As described in the February 2018 issue of Clinical Orthopaedics and Related Research, patients with corticosteroid-induced osteonecrosis had bone marrow-derived stem cells and platelet-rich plasma injected into the femoral head after hip decompression. More than 90% of the 35 hips treated in the preliminary series avoided collapse at a minimum of two years after surgery.

“We don’t necessarily view any of these first-generation orthobiologics — blood, adipose tissue or bone marrow — as definitely better than standard-of-care orthopedic surgery,” Dr. Shapiro says. “For example, patients with severe knee arthritis are probably still best served with knee replacement surgery. But for patients who aren’t good candidates for knee replacements, and haven’t responded to physical therapy or to steroid or hyaluronic acid injections, orthobiologics can fill that treatment gap.”

After visiting the Regenerative Medicine Consult Service, about 10% of patients opt for a cell-based therapy, 25% choose platelet-rich plasma therapy, and the remaining 65% stick with standard-of-care steroid injection, physical therapy or surgery. Whichever approach patients choose, Mayo Clinic tracks treatment outcomes using validated patient-reported measures (Figure 2).

Additional research is underway to refine orthobiologic treatments. Dr. Shapiro is conducting a randomized clinical trial comparing therapy with adipose-derived stromal vascular fraction cells to a saline placebo for the treatment of knee arthritis. That trial builds on previously conducted randomized controlled trials, including a study published in the October 2019 issue of Cartilage. Orthopedic surgeons at Mayo Clinic in Rochester, Minnesota, have undertaken a trial of a stem cell technique, known as RECLAIM, to repair knee cartilage.

“We recognize that our first-generation orthobiologics just scratch the surface in terms of using cells to treat orthopedic disease. The future of orthopedic cell therapy is going to require much more sophisticated versions of these cell therapies,” Dr. Shapiro says. “Treatment using orthobiologics that’s not based in sound orthopedic science is not likely to help people. Mayo Clinic is committed to advancing the science of regenerative medicine, to harness its potential and to provide evidence-based treatments for patients.”

**For more information**


Primary repair remains the treatment of choice for primary patellar and quadriceps tendon rupture. However, extensor mechanism rupture is a more challenging problem in the setting of tendinopathy or previous surgery or in conjunction with a knee dislocation.

Mayo Clinic uses a novel tendon augmentation technique for select patients with these injuries. Described in the May 2016 issue of the *Journal of Knee Surgery*, the procedure consists of a primary patellar or quadriceps tendon repair with semitendinosus autograft augmentation using a proximal or distal patellar socket. Although Mayo Clinic’s original technique preserved the semitendinosus tendon insertion, the current preference is to use a free four-stranded graft (Figure). The benefits include the addition of autogeneic tissue, decreased risk of patellar fracture from transverse or longitudinal bone tunnels, fewer hardware complications, and accelerated rehabilitation.

“It comes down to the fact that normal tendons don’t tear,” says Michael J. Stuart, M.D., an orthopedic surgeon at Mayo Clinic in Rochester, Minnesota. “A tendon with a predisposition to rupture doesn’t have the same healing potential after surgical repair as a normal tendon. Augmentation with a semitendinosus autograft can provide a high-strength construct with distinct advantages.”

Patellar or quadriceps tendon repair and augmentation might be performed for select patients with chronic tendinopathy and poor tissue quality as well as patients with prior tendon debridement or failed primary tendon repair.

“The goal is to improve the patient’s rate of healing with reliable return of extensor mechanism strength and preinjury activity levels,” Dr. Stuart says. “This technique also allows for an accelerated rehabilitation program. Traditionally, if the strength of the repair was a bit tenuous, we would have to immobilize the knee for an extended time with delayed joint motion and strength training. We are confident that the strength of the augmented construct promotes immediate range of motion and progressive resistance strength training with better results and earlier return to work, sports and activities.”

Dr. Stuart cites the case of a 22-year-old professional football player who had undergone right knee patellar tendon debridement for chronic tendinopathy but experienced persistent anterior knee pain with all activities. He achieved full active range of motion six weeks after patellar tendon repair with semitendinosus autograft augmentation surgery at Mayo Clinic. Six months after surgery, the patient resumed all activities without restrictions. Two years after surgery, the patient had retired from football but experienced full knee range of motion and no pain.

“It’s pretty impressive how quickly patients regain knee motion,” Dr. Stuart says. “We have not experienced reoperations, repair failures, hardware complications or patellar fractures to date. The outcomes have been great.”

For more information
Mayo Clinic takes a multidisciplinary approach to managing pediatric congenital hand differences. Hand surgeons collaborate with highly experienced pediatric anesthesiologists when surgery is indicated. Children whose anomalies may be associated with a specific syndrome can be seen by Mayo geneticists and other specialists. All pediatric patients can seamlessly transition to adult care at Mayo when the time comes.

“We seek to provide the right answer with a single visit. When needed, we have all of our specialists here on campus so families can get plugged into seeing the right people quickly,” says Nicholas A. Pulos, M.D., an orthopedic surgeon specializing in pediatric hand and microvascular surgery at Mayo Clinic in Rochester, Minnesota. “Our approach is to address every aspect of care — from diagnosis to treatment to emotional support — so the family feels well taken care of.”

Managing complex and straightforward conditions
Early referral is key to optimal outcomes. Complex conditions such as radial longitudinal deficiency can be associated with life-threatening pathologies and syndromes. More-straightforward problems, such as postaxial polydactyly, can often be treated right away in the office. However, Mayo Clinic recommends evaluation by a pediatric hand surgeon who can determine if surgery might be beneficial.

“Without a lot of experience with these cases, it’s sometimes difficult to know which children need surgery and when,” Dr. Pulos says. “Based on our experience, we like to assess these children early to avoid future complications.”

Mayo Clinic also performs reconstructive surgery for children born with syndactyly. Hand surgery is generally performed between 2 and 3 years of age to minimize risks from anesthesia, although surgery for conditions involving the thumb might be performed earlier. Mayo Clinic has fellowship-trained pediatric anesthesiologists who have published extensively in the field.

“My son had surgery at age 6 months, so I know how anxiety-provoking it can be for parents to have a child under anesthesia. We are able to provide reassurance,” Dr. Pulos says.

Another common problem is stenosing tenosynovitis, which in children affects the thumbs more often than other fingers and is sometimes called trigger thumb. “Although trigger thumb may resolve over time, the thumb doesn’t always return to normal on its own. Also, fingers are often more complicated in children than in adults,” Dr. Pulos says. “This is another condition where evaluation by an experienced hand surgeon can help determine whether surgery is appropriate. Depending on the child’s age and how long the child has had trigger thumb, we can make a shared decision with the parents about whether the child should undergo surgery.”

Follow-up care for children with hand anomalies involves occupational therapy and support. “We want to make sure, before kids start formal schooling at age 5, that they can keep up with their peers to the best of their abilities,” Dr. Pulos says. “As children mature, we try to ensure that they can do sports or other after-school activities that bring them pleasure, and that they feel comfortable with their hand differences. We also see children at skeletal maturity to make sure they’re achieving their goals. After that, we are able to follow these children into adulthood.”

The goal is to provide all aspects of care needed by children with hand differences and to provide support for their families. “Parents are understandably very anxious when a child has a congenital hand difference,” Dr. Pulos says. “We are happy to talk to parents during the first months of their child’s life to discuss these concerns and to help answer questions about their child’s future.”
Mayo Clinic is one of the few centers that uses free vascularized fibula grafts (FVFGs) for reconstruction after tumor resection in the spine and pelvis. Surgical teams that include orthopedic oncology surgeons as well as hand and plastic surgeons have performed more than 60 of these complex procedures, with generally favorable outcomes.

“We have achieved a union of the spine and pelvis in more than 90% of these patients,” says Peter S. Rose, M.D., an orthopedic surgeon at Mayo Clinic in Rochester, Minnesota. “It’s a long and complex procedure, but it’s very well suited for patients who are undergoing a curative tumor resection — particularly patients with a strong potential for long life expectancy. They need a durable reconstruction, and the vascularized graft provides healing potential.”

Reconstruction of the spine after tumor resection frequently requires surgeons to address large osseous defects and compromised bone healing due to radiation and chemotherapy. In the treatment of lower spinal and sacral tumors, resection often disrupts continuity between the spine and pelvis, resulting in severe biomechanical disadvantages, including the inability to transfer the load of the body to the lower extremities.

Although FVFG transfer has long been performed successfully for lower extremity reconstruction, the procedure’s use in the spine and pelvis has been limited. Mayo Clinic’s approach uses an FVFG alone or in combination with a structural allograft or reconstruction cage.

When used alone, the FVFG is sometimes cut and layered to make it more robust (Figure). “We double-barrel or even triple-barrel configurations to increase the strength of the vascularized graft,” Dr. Rose says.

Combining an FVFG with an allograft provides even greater bulk, as well as the capacity for osteogenesis. “Putting the two together works very well when we have to cut the side of the femur, for example,” Dr. Rose says. “We need something that can bear the patient’s whole weight after surgery. But if we use an allograft alone, the patient has difficulty healing and is prone to develop stress fractures over time. As a living bone, the fibula graft has much greater healing potential and can promote healing of a stress fracture if that happens.”

The advantages of vascularized bone transfer are particularly noteworthy in the setting of radiotherapy. Mayo Clinic’s treatment protocol for many cases of spinal tumor involves proton beam or other high-dose radiation therapies.

“These radiotherapies have very good efficacy for treating the cancer but are highly damaging to bone,” Dr. Rose says. “The docking sites for the graft are irradiated, which compromises the graft’s ability to heal. A vascularized bone transfer helps us overcome that problem.”

Mayo Clinic has also demonstrated favorable results with the use of FVFGs for pediatric limb salvage. In a study published in the October 2018 issue of *Plastic and Reconstructive Surgery*, Mayo Clinic researchers found that FVFG supplementation reduced the risk of allograft revision for children undergoing lower extremity reconstruction. The researchers compared the outcomes of 29 pediatric patients who had lower extremity limb salvage using intercalary cadaveric allografts. Eleven patients had reconstruction using allografts alone; 18 had allografts supplemented with FVFGs. Three patients subsequently required allograft revision because of fracture or fracture and infection. However, none of those three allografts had FVFG supplementation.

“One of the patients in this study had to have a secondary bone graft procedure. But we ultimately achieved union in nearly every one of these children,” Dr. Rose says.

Mayo Clinic’s extensive experience with vascularized bone transfers has allowed its surgeons to apply...
Mayo Clinic has developed a unique revision surgery for people who experience a failed first metatarsophalangeal joint replacement. The revision procedure involves removal of the implant and reconstruction of the great toe to restore function and relieve pain.

“Over the last 14 years, our procedure has had a very high success rate,” says Joseph L. Whalen, M.D., Ph.D., an orthopedic surgeon at Mayo Clinic in Jacksonville, Florida.

Joint replacement is sometimes offered as a treatment option for metatarsophalangeal arthritis, a condition that severely affects the ability to walk and to wear shoes comfortably. “Toe arthritis can be every bit as disabling as ankle arthritis or knee arthritis,” Dr. Whalen says.

Mayo Clinic’s approach to toe arthritis usually involves fusion surgery — the gold standard of treatment. However, people who undergo toe fusion can experience pain if they wear shoes with heels higher than an inch. That restriction prompts some people to seek joint replacement, often from a podiatrist, for the treatment of toe arthritis.

“When those joint replacements fail, it’s a difficult reconstructive problem,” Dr. Whalen says. “We can’t just take out the implant because joint replacement surgery removes a lot of bone. The big toe is significantly shortened — it’s usually shorter than the second toe by one-third — which leads to transfer metatarsalgia. Often the big toe sticks up and won’t touch the floor. It’s very painful.”

Mayo Clinic’s salvage surgery (Figure) uses an interpositional graft that has been contoured from a patella wedge. “The density of that bone allows us to fill the bone defect after we remove the implant from the big toe. We can generally lengthen the toe by 10 to 12 millimeters, which is enough to relieve the transfer metatarsalgia,” Dr. Whalen says.

The precise amount of toe lengthening depends on factors such as soft tissue scarring and the patient’s circulatory health. The structural bone graft fully incorporates by about eight to 16 weeks after surgery. Successful healing occurs in approximately 90% of patients who comply with postoperative restrictions.

Dr. Whalen notes that revision surgery can be avoided if patients with metatarsophalangeal arthritis opt for fusion surgery, which generally provides positive outcomes.

“There are many misconceptions about fusing the big toe,” he says. “People think they’re going to limp or walk abnormally after the surgery, so they avoid it. But fusion provides highly predictable pain relief. Patients who have the procedure are generally very happy with the results.”

Salvage Surgery for Failed Toe Joint Replacement

Joseph L. Whalen, M.D., Ph.D.

Figure. X-rays illustrate the case of a patient who presented at Mayo Clinic in Jacksonville, Florida, with severe stiffness and pain after a first metatarsophalangeal joint replacement. On the left, a preoperative X-ray shows a 1.4-centimeter shortening of the great toe of the left foot, where joint replacement had been performed. On the right, an X-ray three months after revision surgery at Mayo Clinic shows the healed bone graft and restored toe length. The patient is now pain-free.
Mayo Clinic is investigating infrapatellar saphenous nerve neuroma as a source of pain after total knee arthroplasty. About 20% of patients who have a total knee arthroplasty are dissatisfied with the result, often due to residual pain. Mayo Clinic’s work seeks to address persistent medial knee pain that lacks a clear etiology, such as infection, misalignment or loosening of the prosthesis.

“This type of medial pain can be misdiagnosed as tendonitis or pes anserine bursitis. But it often turns out to be an infrapatellar saphenous nerve neuroma that is causing pain,” says Glenn G. Shi, M.D., an orthopedic surgeon at Mayo Clinic in Jacksonville, Florida. “Patients who have a misdiagnosis might be sent to pain clinics or physical therapy with no reasonable outcomes. That leads to a lot of frustration for patients and orthopedic surgeons alike.”

The incidence of infrapatellar saphenous nerve neuroma after total knee replacement is unknown. “But we think this problem is underrecognized,” Dr. Shi says.

In cadaveric studies, Mayo Clinic has found that the standard surgical incision used in total knee arthroplasty almost always severs the infrapatellar saphenous nerve (Figure). The severed nerve generally doesn’t affect the knee’s function. But the nerve ending can become trapped in the incision’s closure or in subsequent scar tissue, leading to a neuroma.

“Why some people get a neuroma and others don’t is part of our investigation,” Dr. Shi says. “We are also trying to determine if we can somehow tuck the nerve end into the knee during surgery, to protect it from entrapment and prevent problems down the road.”

Seeking a modified surgical technique
Mayo Clinic’s investigation of saphenous nerve neuroma after total knee arthroplasty encompasses several studies. The cadaveric project aims not only to understand the anatomical pattern of the nerve’s intersection with a standard knee-replacement incision but also to investigate suturing techniques that avoid trapping the nerve in the incision closure. Clinical studies assess how frequently orthopedic surgeons see the saphenous nerve during standard total knee arthroplasty. “If we can teach our orthopedic surgeons to see the nerve, we can potentially avoid injury that might require another surgery,” Dr. Shi says.

Figure. Illustration shows the infrapatellar branch of the saphenous nerve, which is typically severed during total knee arthroplasty.

In addition, Mayo Clinic is investigating strategies to treat infrapatellar saphenous nerve neuroma. One approach involves ultrasound-guided hydrodissection of the nerve from the adjacent interfascial planes, followed by a corticosteroid injection. A preliminary Mayo Clinic study found that this minimally invasive procedure significantly reduced medial knee pain for nine of 16 patients studied.

For patients whose pain persists after hydrodissection, Mayo Clinic is exploring options for surgical repair. “We are trying to use a less invasive incision to find the nerve end and place it in an area where it is protected from scar tissue,” Dr. Shi says. A prospective study is using a similar approach during total knee arthroplasty to prevent infrapatellar saphenous nerve neuroma from developing.

“This problem isn’t widely discussed among orthopedic surgeons, but it’s very impactful. Up to 3 million people are expected to have total knee arthroplasty by 2035,” Dr. Shi says. “Our goal is to bring attention to this problem, which we think contributes to patients’ dissatisfaction after total knee arthroplasty. A modified technique for the procedure can potentially avoid the development of neuroma and reduce pain.”
Education Opportunities

For more information or to register for courses, visit https://ce.mayo.edu/group/orthopedic-surgery, call 800-323-2688 (toll-free) or email cme@mayo.edu.

4th Annual Sports Medicine for the Primary Care Clinician 2020
March 6-8, 2020, in Orlando, Fla.
This course supplements skills learned in residency, by filling in gaps in training and reinforcing existing knowledge of musculoskeletal conditions, diagnosis and treatment. The goal is to provide attendees with the confidence to accurately diagnose and treat sports-related conditions, and the knowledge to determine appropriate testing and referral criteria. The course also helps improve skills in physical examination and imaging interpretation to assist in the prompt determination of conditions that may have implications for sports and recreational physical activities. This course is designed for athletic trainers, physical therapists, nurse practitioners, physician assistants, sports medicine physicians, physiatrists, internists, pediatricians, emergency room physicians and orthopedists, in addition to family physicians.

9th Annual Comprehensive Sports Medicine Update and Board Review 2020
June 17-20, 2020, in Minneapolis
This award-winning course provides a comprehensive review of all subjects contained in the sports medicine board examination. The faculty include internationally recognized experts in the field of sports medicine. This course is designed for physicians who practice sports medicine, internal medicine, pediatrics, orthopedics, family medicine, emergency medicine, or physical medicine and rehabilitation. Physician assistants, athletic trainers, nurse practitioners, physical therapists and chiropractors also will benefit from attending the course.