Musculoskeletal Injuries and Regenerative Medicine in the Elderly Patient

John C. Cianca, MD[a,*], Prathap Jayaram, MD[b]

KEYWORDS

• Regenerative medicine • Platelet-rich plasma • Stem cell therapy • Prolotherapy
• Osteoarthritis

KEY POINTS

- Regenerative medicine is an emerging field that has value in musculoskeletal injuries and conditions in the elderly.
- Viscosupplementation and prolotherapy are established therapies that continue to show efficacy in the elderly population.
- Platelet-rich plasma injections and mesenchymal stem cell therapy are emerging therapeutic strategies that have shown a good safety profile.

INTRODUCTION

Regenerative medicine has gained increasing popularity in its clinical applications, particularly in the field of musculoskeletal medicine. Regenerative medicine, a broad term, can be thought of as a particular medical strategy that strives to rebuild and restore diseased tissue to normal physiologic tissue baseline. Simply put, regenerative strategies augment the body's innate physiology to heal pathologic processes.[1] This article focuses on specific regenerative strategies and the uses of them for common pathologies in the aging adult, including platelet-rich plasma (PRP), mesenchymal stem cells (MSCs), viscosupplementation, and prolotherapy.

COMMON CONDITIONS AFFECTING THE ELDERLY

Tendinopathy

Tendinopathy is common degenerative condition seen in all adults, but in particular in tendons of the elderly. Tendinopathy is thought to result primarily from a blunted

The authors have nothing to disclose.
[a] Department of Physical Medicine and Rehabiltation, Baylor College of Medicine, University of Texas Health Science Center, 1 Baylor Plaza, Houston, TX 77030, USA; [b] Department of PM&R and Orthopedic Surgery, Regenerative Sports Medicine, Baylor College of Medicine, 1 Baylor Plaza, Houston, TX 77030, USA
* Corresponding author. Human Performance Center, 5959 West Loop South, Suite 260, Bellaire, TX 77401.
E-mail address: john.cianca@hpchouston.com

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inflammatory response to tendonitis, leading to a degenerative cycle of abnormal healing.[2] Chronic repetitive tendon overload is the most commonly proposed theory, with high loads causing microscopic alterations at the cellular level that weaken the mechanical properties. Aging can result in progressive loss of mobility with subsequent deterioration in quality of life. A major component of this loss of mobility is progressive muscle weakness, as elderly muscles become smaller, more susceptible to damage, and regenerate and recover more slowly than in their youth.[3] Only recently has it been recognized that, in addition to skeletal muscle changes, alterations in tendon properties contribute to muscle weakness and loss of mobility in old age.[3]

Rotator cuff tendinopathy

Rotator cuff tendinopathy is the most common cause of shoulder pain in all age groups, accounting for 30% of shoulder related pain.[4] It arises from the repetitive strain incurred by overuse and poor postural control because the rotator cuff acts in its role as the primary dynamic stabilizer of the glenohumeral joint. Clinical features of rotator cuff tendinopathy include pain, crepitus, and increased pain with overhead activities of daily living. In a study done by Milgrom and colleagues,[5] the prevalence of RTC tears markedly increased after 50 years of age, with more than 50% of dominant shoulders in the seventh decade and 80% of subjects greater than 80 years of age. Riley and colleagues[6] demonstrated that the supraspinatus tendon undergoes a decrease in glycosaminoglycan, chondroitin sulfate and dermatan sulfate with age. In another study by Rudzki and colleagues,[7] regional variations in supraspinatus tendon vascularity were shown in an age-dependent manner. These results support that, even without clinical symptoms, the aging shoulder is likely to transition to attritional tendinopathy, perhaps making the shoulder more susceptible to injury.

Gluteal tendinopathy

Gluteal tendinopathy commonly presents as pain and tenderness laterally over the greater trochanter (lateral hip pain). It is a cause of moderate to severe pain and disability,[8–11] with 1 study demonstrating quality of life and levels of disability similar to those in end-stage hip osteoarthritis (OA).[12] Gluteal tendinopathy is most prevalent in women aged greater than 40 years[13,14] with reports of up to 23.5% of women and 8.5% of men between the ages of 50 and 79 years being afflicted with condition.[14] It is the most prevalent of all lower limb tendinopathies.[15] The mechanism leading to its development is multifactorial. Load shear strain, as mentioned, is a particular contributing factor. The influence of joint position affects compressive tendon loading from excessive hip adduction.[16] Patients with gluteal tendinopathy may experience pain after prolonged sitting, with subsequent difficulty in rising to standing, particularly if they have been sitting with more than 90° of hip flexion in a low lounge or car seat. Surrounding muscle architecture also plays a role in development of tendon pathology: the tensor fascia lata has been shown to hypertrophy[17] and gluteus medius and gluteus minimus atrophy[18] in those with gluteal tendon pathology. Bone morphology influences the compressive forces at the hip by vectors from the iliotibial band. The typical femoral neck angle of 128°, the iliotibial band exerted a compressive force of 656 N at the greater trochanter, but at 115° (coxa vara), the compressive force was 997 N.[19] These findings suggest that patients with more severe gluteal tendon pathology have lower femoral neck–shaft angles than pain-free controls or those with hip OA.

Knee extensor mechanism tendinopathy

Patellar tendinopathy, also referred to as jumpers knee, results from chronic tendon overuse and overload of the knee extensor mechanism. The most common location

of pain is the superior patellar pole for the quadriceps tendon and the inferior patellar pole in the patellar tendon. The exact etiology is not well-established; however, it is thought to be due in part to peripheral peritendinous pain receptors or the neovascularization that occurs after injury.[20,21] Risk factors are thought to include poor hamstring and quadriceps flexibility, poor knee joint coordination, reduced ankle dorsiflexion, and increased pronation velocity of the foot.[22] There is some controversy regarding how aging affects patellar tendon collagen cross-linking. Couppe and colleagues[23] showed that human patellar tendon collagen concentration was reduced, whereas cross-linking of concentration was elevated in elderly men versus younger men, which may be a mechanism to maintain the mechanical properties of tendon with aging. Another study looking at aging effects on patellar tendon showed that patellar tendon mechanical properties at maximal force are altered with aging, and these differences are more related to force output rather than to an age effect.[24]

Achilles tendinopathy Achilles tendinopathy is a common clinical condition that affects the elderly and is characterized by pain and swelling in the middle and distal portions of the Achilles tendon. The development of tendinopathy once again is thought to be due to overuse and repetitive loading. Intrinsic risk factors in the elderly are thought to be decreased ankle dorsiflexion range of motion, abnormal subtalar range of motion, decreased plantar flexion strength, excessive foot pronation, and poor tendon vascularity.[25] Recent work in ultrasound using elastography has shown increased stiffness in elderly subjects, which may be a contributing factor for the high prevalence of Achilles tendinopathy observed in elderly patients.[26]

Degenerative Joint Disease

OA is a common clinical condition with a prevalence of 40 million people in the United States. More than 80% of individuals over the age of 55 have radiographic evidence of OA. Among those, 30% of the individuals present with significant pain or disabilities.[27] This equates to 5.6 million individuals in the United States and corresponds with an annual expenditure of $3 billion for posttraumatic arthritis.[28] However, current treatment of OA is limited to lifestyle modification, analgesics, and invasive procedures such as joint replacement surgery in severe cases. The mechanism and important biological contributors in OA remain largely unknown. Therefore, new clinical strategies that may improve the evaluation and augment repair and regeneration of damaged articular cartilage that prevent or delay the onset of disabling pain and OA have become a increasingly prevalent clinical strategy.

Degenerative Disc Disease

Increases in life expectancy will lead to a higher number of elderly people.[29] According to the United Nations Population Fund, people aged 60 years and older made up more than 11% of the global population in 2012, a proportion that will increase to about 22% by 2050.[30] Consequently, physicians will face an ever-increasing number of elderly patients suffering from degenerative processes such as degenerative disc disease in the future. Low back pain is a very common cause of pain in the elderly that affects up to 80% of adults at some time during their life. In people over 55 years of age, 95% of lumbar disc herniations occur at the L4 to L5 and L5 to S1 levels.[31–34] Early nonoperative intervention is always attempted first; however, there are cases where surgical intervention is necessary. Long-term outcomes after surgery remain a controversial topic, which has created a role for regenerative strategies.

Spinal Stenosis

Lumbar spinal stenosis refers to narrowing of the lumbar spinal canal either centrally, laterally, or at the neural foramina. The narrowing is associated with neural compression, and clinically most often manifests fatigue with walking or standing, weakness, or radicular pain in 1 or both legs. Lumbar spinal stenosis has an annual incidence of near 5 per 100,000.[35] The prevalence increases with age, and is suggested to be between 1.7% and 8.0% in the general elderly population.[35] It is the most common diagnosis leading to spinal surgery in patients over the age of 65. Approximately 1 in 1000 people over the age of 65 have had a laminectomy for lumbar spinal stenosis, with an estimated cost of $1 billion.[36] There are no regenerative strategies to date that target the central stenosis etiology, but surrounding structural changes of facet arthrosis have been targeted.

REGENERATIVE TREATMENT STRATEGIES FOR MUSCULOSKELETAL CONDITIONS

Viscosupplementation: Historical Perspective and Use

Hyaluronate is a naturally occurring component of the cartilage and the synovial fluid. It is a polysaccharide composed of continuously repeating molecular sequences of β-D-glucuronic acid and β-d-*N*-acetylglucosamine, with a molecular mass in normal synovial fluid ranging from 6500 to 10,900 kDa.[37] Within the normal adult knee, there is approximately 2 mL of synovial fluid, with a hyaluronate concentration of 2.5 to 4.0 mg/mL.[38] Hyaluronate is responsible for lubricating and potentially reducing shear forces within the knee joint, depending on the forces exerted on it.[39] In OA, synovial hyaluronate is depolymerized and cleared at higher rates than normal.[40] In a normal joint, the average intrasynovial half-life of hyaluronate is approximately 20 hours.[38] In an inflamed joint, this half-life is decreased to 11 to 12 hours. These changes reduce the viscoelasticity of the synovial fluid.

Viscosupplementation is an exogenous hyaluronate that was developed as a treatment for the symptoms of knee OA. Viscosupplementation can be thought of as a first-generation biologic strategy; it can be either synthesized by means of bacterial fermentation or extracted from animal tissues (eg, rooster comb). The therapeutic goal of administration of intraarticular hyaluronate is to provide and maintain intraarticular lubrication, and increase the viscoelastic properties of synovial fluid[41]; Another proposed mechanism is that hyaluronate exerts antiinflammatory, analgesic, and possibly chondroprotective effects on the articular cartilage and joint synovium.[38] The clinical benefits of treatment with intraarticular hyaluronate, which persist well beyond the intraarticular residence time of the product, have been suggested to be caused by the reestablishment of joint homeostasis as a result of an increase in the endogenous production of hyaluronate that persists long after the exogenous injected material has left the joint.[40]

There is no clear supporting evidence of clinical criteria to select patients who will likely benefit from hyaluronate injections. However, trial data suggest that patients with late-stage disease (such as those with marked joint space narrowing) who are older than 65 years of age are less likely than younger patients or patients with earlier disease to have any benefit, that is, the lower the grading in the Kellgren Lawrence scale, the greater the effect of viscosupplementation.[42]

Tenotomy

A mechanical treatment technique that is used primarily for tendons, tenotomy is analogous to trigger point work in muscles. It is alternatively referred to as tendon fenestration or dry needling. The goal is to target pathologic changes within a tendon with

the intention of initiating a healing response. A hypodermic needle is introduced into the tendon guided by ultrasound imaging. The needle is repeatedly advanced and withdrawn within the pathologic portion of the tendon. Ultrasonographic guidance allows the needle to be placed precisely within the area of pathology. This is done by viewing the needle in plane first as it enters the tissue. Once localized to the area of pathology, the ultrasonographic transducer is turned 90° out of plane with the needle, providing a cross-sectional view of the pathologic area. The needling action is continued in a back and forth motion with redirection across the width of the area of pathology, as seen with the transducer. The needle is out of plane with the transducer and only the tip is seen as it advances in and out of the tissue (**Figs. 1** and **2**). This process introduces injury to the tendon tissue, invoking bleeding and an acute inflammatory response in the region. If the area of pathology is in an enthesis, then the bony insertion is needled as well. The needle action causes bleeding from both tissues and this mechanism of injury induces an acute inflammatory reaction mediated by a variety of growth factors and in so doing the tendon may be able to remodel and heal.[43] Tenotomy is frequently used with other regenerative techniques, such as prolotherapy and PRP. These entities further support a healing process by providing substrates locally to the tendon, which often has a limited blood supply. Compared with surgical treatment, it is less expensive and has a lower rate of associated adverse events. Tenotomy proved effective for reducing pain in lateral epicondylosis and several other tendinopathies.[44]

A retrospective study 82% of patients treated with tendon fenestration for tendinopathy of the gluteus medius, minimus, proximal hamstring, or the tensor fascia lata showed marked improvement.[45] The tendon fenestration technique has been demonstrated to be effective in a prospective study on a variety of tendinopathic conditions measuring pain using a visual analog scale.[46]

Tenotomy has been shown to be effective used alone for treatment when compared with its use with steroid.[47] In another study, PRP with tenotomy had a greater effect initially but was no more effective than tenotomy alone after 6 months.[48]

Other needle techniques that have been reported to have a reparative effect on tendinopathy include tendon scraping[49] to disrupt neovascular tissue and the associated nerve ingrowth into chronically affected tendons. Disrupting these nerves is thought to have a pain-relieving effect. Using shock waves and rapidly oscillating percutaneous needling has also been shown to have similar effects as needle fenestration.[50]

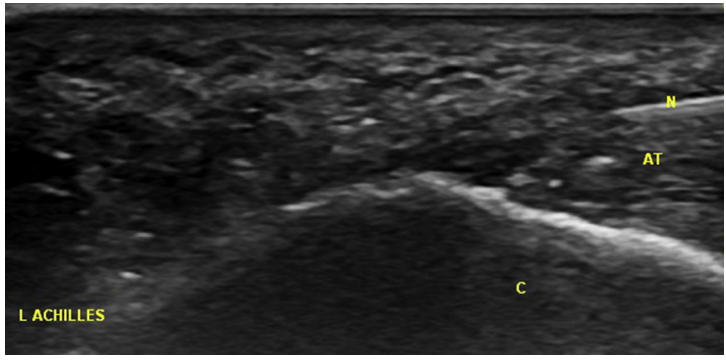

Fig. 1. Needle viewed in plane. An in-plane view of a needle approaching the Achilles tendon insertion during a tenotomy. AT, Achilles tendon; C, calcaneus; N, Needle. *Courtesy of* John C Cianca, MD, Baylor College of Medicine, University of Texas Health Science Center, Houston, TX.

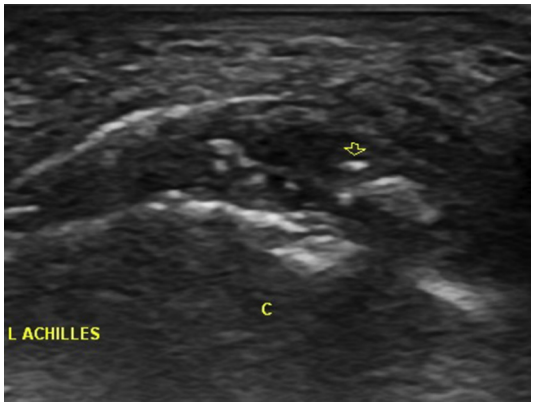

Fig. 2. Needle viewed out of plane. An out-of-plane view of a needle in the Achilles tendon during a tenotomy. C, calcaneus; arrow head, needle tip. *Courtesy of* John C Cianca, MD, Baylor College of Medicine, University of Texas Health Science Center, Houston, TX.

Prolotherapy

Prolotherapy as it is now known originally was called sclerotherapy. Sclerotherapy had its origins in 16th century France. Chemical irritants were injected into incompetent or lax ligaments resulting in fibrous tissue formation (scar) and promoting structural stability in the tissue.[51] Hackett[52] began using less noxious injectants in the mid-20th century resulting in proliferation of the affected tissue. He began referring to this technique as prolotherapy so as to differentiate it from the sclerotherapy technique. Prolotherapy evolved during the later decades of the 20th century and during the early years of the 21st century.[52] Hackett's original research demonstrated an increase in the size of tendon and tendon enthesis in an animal model 2 weeks after treatment.[53] As the treatment technique has evolved, it has been used more liberally in a variety of tissues and conditions. Early formulations included synasol and sodium murrhuate and a formula of phenol, glycerin, and glucose.[54] Dextrose is the agent of choice in current clinical practice. Local anesthetic as well as sterile water or normal saline are added to 50% dextrose creating formulas with as high as 25% dextrose and as low as 5% dextrose.

It is commonly believed that these proliferants cause an osmotic gradient with the target tissue leading to cell desiccation and an inflammatory response. Growth factors are released within the tissues as a result, leading to a healing response.[55,56] Furthermore, it is postulated that dextrose serves as a signaling agent in tendon repair.[55] As such, it may be considered the first injectable regenerative medicine agent.

As a prerequisite, the patient should be withdrawn from nonsteroidal antiinflammatory drugs for 2 to 3 days before treatment to allow the inflammatory response to be initiated. The injection technique uses small gauge needles, generally 25 to 30 gauge, advancing into and around the tissue. Once in the tissue, a tenotomy-like action is often used followed by injection of the dextrose solution in small aliquots (less than 1 mL per site). Additionally, where applicable, bone stimulation is done. This has been postulated to result in additional release of chemical mediators of injury. The upregulation of a variety of growth factors specific to ligaments and tendons as well as cartilage have been identified.[57] When accurately delivered, the treatment is safe and only minimally painful. After the procedure, patients may have soreness or mild to moderate pain owing to the induction of an inflammatory response. Resting the

affected tissue from impact and repetitive use or loading is recommended. Gentle passive or active assisted motions are encouraged. Nonnarcotic pain relievers such as acetaminophen are usually sufficient if needed. Nonsteroidal antiinflammatory drugs should be avoided for 7 to 10 days.

Back pain is prevalent in middle-aged and senior adults. OA of the spine, degenerative disc disease, and spinal stenosis are all prevalent diagnoses. Sacroiliac joint, coccydynia, and ligamentous causes of back pain are also common. Prolotherapy has been used to treat low back pain for many decades.[52,53,58–60] More recent studies have demonstrated greater duration in pain relief than steroid in the sacroiliac joint.[55] Prolotherapy resulted in extended pain relief in patients with discogenic pain with or without radicular pain in another study.[61]

OA is a significant cause of functional decline and disability. It is also a considerable driver of health care costs in the aging adult. The use of prolotherapy in recent years to treat osteoarthritic joints has had encouraging results. Studies using animal models have demonstrated a chondroprotective effect of intraarticular dextrose injections.[62] Randomized, controlled trials have demonstrated pain reduction and functional improvement in humans.[63–65] Most recently, pain reduction and functional improvement as well as chondrogenesis was demonstrated in a case series.[66] Additionally, studies of have demonstrated clinical improvement in OA of the thumb[63]

Treatment protocols for OA rely on intraarticular injections of dextrose solutions ranging from 12.5% to 25%. Cessation of nonsteroidal antiinflammatory medications before treatment and after treatment is recommended as with other prolotherapy regimens. Rest from weight bearing exercise for several days is encouraged. Treatments are usually administered at monthly intervals for 2 to 4 months.

In addition, adjunctive superficial injections of dextrose solutions may be done along the affected joint surface. Now known as perineural injection therapy, this technique targets superficial nerves in the region of pathology. It is purported that these superficial nerves are responsible for neurogenic inflammation that can cause a chronic upregulation of pain via the activation of transient receptor potential vanilloid 1 channels, leading to chronic pain and soft tissue dysfunction. Injection of 5% dextrose around these nerves can stabilize nerve function reducing neurogenic inflammation.[67]

People in general and older adults in particular have been encouraged to be more active to promote health. However, with an increasing level of activity, there is likely to be a greater incidence of overuse injuries and pathologies. The occurrence of tendon pathology has become clinically relevant. Several studies have been done demonstrating pain relief and functional improvement in patients with common extensor tendon, and patellar and Achilles tendinopathies as well as plantar fasciopathy.[68–72] Prolotherapy compared favorably with PRP in the treatment of chronic plantar fasciitis.[73] A systematic review of several case series and controlled trials found prolotherapy, PRP, polidocanol, and autologous whole blood to be effective in the treatment of lateral epicondylosis.[68] In addition, 1 study demonstrated structural improvement in the patellar tendinopathy.[69]

The safety profile of prolotherapy has been established and, owing to its inexpensive treatment technique, provides an alternative treatment option. It is being used with greater frequency in clinical medicine. Nonetheless, more robust research needs to be done. Although evidence is growing and becoming more substantive, much of the research has been case reports and uncontrolled trials.[74] It has usefulness in a variety of conditions that are common and likely to become more prevalent as people live longer and become more active.

Platelet-Rich Plasma

PRP is a derivative of autologous blood containing a higher than physiologic concentration of platelets.[75] To date, there is no standard protocol for PRP formulations. The efficacy of PRP is, therefore, likely impacted by the composition of the PRP itself. This can lead to high degrees of variability in comparing the efficacy of PRP across clinical studies. Several classification systems for PRP have been proposed, although none have been widely accepted.[76–78] In an attempt to better understand clinical efficacy, this classification has been suggested to categorize the type of PRP injected.[79]

Preparations

PRP preparation requires 15 to 100 mL of whole blood obtained via peripheral venipuncture, depending on the commercial method being used. PRP is prepared by centrifugation of anticoagulated whole blood. It is initially separated into 3 layers based on specific gravity: (1) plasma (top layer), (2) platelets and leukocytes (middle layer, termed the "buffy coat"), and (3) red blood cells (bottom layer). The bottom layer is typically discarded; the buffy coat and top layer are then often subjected to a second centrifugation to separate PRP from platelet-poor plasma. PRP may then be activated with calcium chloride or thrombin to cause the release of growth factors from alpha granules to occur more rapidly, although this additional step is not performed universally. Different harvesting and centrifugation methods yield different volumes and concentrations of platelets.[80] There is also great variability in the timing of PRP acquisition. It has been shown that PRP samples produced from the same patient, using the same centrifugation protocol and equipment, may lead to PRP of varying composition.[81]

Applications

There has been an increase in the usefulness of PRP for degenerative musculoskeletal conditions in the last decade. Given the lack of reported studies characterizing PRP, it becomes difficult to support a specific level of evidence and clinical recommendation. However, there is level 1 evidence to support its use in lateral epidcondylosis and tendinopathy, as well as OA of the knee.[82] Although lateral elbow tendinopathy does not affect the elderly population as frequently as younger populations, its degenerative mechanism of tension loading and failure to remodel is akin to other prevalent tendinopathies in the elderly. Corticosteroids, which have been widely used in the past, have been shown to have a deleterious effect on tendon and joint tissue.[83] In contrast, the use of such agents as PRP, which may stimulate tissue healing and have no deleterious effects, seem to be a more reasonable choice. PRP applications to elderly rotator cuff dysfunction has not been supported by high level evidence. However, in recent years there has been an increase in studies involving operative rotator cuff repairs[83–86] and some evidence to support its use in direct treatment of RTC injuries.[87]

In general, evidence for the effectiveness of PRP remains weak. In a prospective, randomized, double-blind study, Weber and colleagues[84] compared recovery from arthroscopic rotator cuff repair with and without application of a platelet-rich fibrin matrix and found no differences in range of motion, pain, and rate of retear at multiple time points up to 12 weeks postoperatively. In another prospective cohort study, Jo and colleagues[85] found that treatment with PRP did not enhance arthroscopic rotator cuff repair in terms of discomfort, strength, movement, function, or satisfaction after 16 months. Similarly, Bergeson and colleagues[86] were unable to show the benefits of a platelet-rich fibrin matrix for arthroscopic rotator cuff repair in comparison with controls. Kesikburun and colleagues[87] compared PRP with saline for the treatment of chronic rotator cuff tendinopathy and found significant improvement in both groups, with sizable improvements in both pain and function. Rha and colleagues[88] compared

ultrasound-guided PRP injection with dry needling. Dry needling or 2 PRP injections were performed 4 weeks apart and significant improvement was found in the Shoulder Pain and Disability Index scores, passive internal rotation, and flexion of patients treated with PRP as early as 6 weeks, which continued until 6 months after injection. These studies were not restricted to an elderly population and more conclusive studies need to be done before providing a recommendation.

Studies of gluteal tendinopathy, although highly prevalent in the elderly, has yielded little evidence to support the use of PRP. A recent study by Lee and colleagues[89] studied 21 patients prospectively who all received 1 guided PRP injections for recalcitrant tendinosis and/or partial gluteus medius tears with significant improvement in subjective outcomes. Given how prevalent this pathology is, more robust studies need to be done before this can be recommended strongly.

Patellar tendinopathy has been studied more robustly compared with gluteal tendinopathy, however, not exclusively in the elderly. Kon and colleagues[90] evaluated the effects of a series of 3 PRP injections, each given 15 days apart, with significantly improved overall function, pain, perception of physical and emotional health, vitality, and a sense of limitation at 6 months. James and colleagues[91] looked at the usefulness of 2 injections of autologous blood at 4-week intervals, in combination with dry needling, demonstrating significant improvement in the Victorian Institute of Sports Assessment score at follow-up, which averaged approximately 15 months. In a recent systematic review by Everhart and colleagues,[92] examining 15 studies their conclusion for initial patellar tendinopathy treatment should consist of eccentric squat-based therapy, shockwave, or PRP as monotherapy or an adjunct to accelerate recovery. Reproducible and comparative clinical results are lacking, owing to at least in part to the variety of PRP preparations and treatment methods.

There is an established safety profile for PRP applications in Achilles tendinopathy, but strong evidence with respect to clinical efficacy is lacking. In a randomized, placebo-controlled trial comparing PRP with saline injection, De Vos and colleagues[93] demonstrated statistically significant improvement compared with baseline for pain and level of activity, based on Victorian Institute of Sports Assessment Score A. Sanchez and colleagues[94] looked at the ability of platelet-rich fibrin to enhance healing of surgically repaired Achilles tendon ruptures, demonstrating improved ankle motion, and faster return to gentle running and sport. Moreover, subjects treated with platelet-rich fibrin returned to preinjury activity levels at a mean interval of 14 weeks, an average of 8 weeks earlier than controls.

Stem Cell Therapies

Stem cell theory

MSCs, also called mesenchymal stromal cells, are adult stem cells that are multipotent and located throughout the body (**Fig. 3**). They are multipotent in that they self-renew for long periods of time and differentiate into specialized cells with specific functions, but are limited in ability to differentiate.[95] The exact regenerative mechanism of MSCs role remains unclear; however, it is believed that a primary purpose of MSCs is to replace lost or damaged cells and tissues within their local environment.

Definition

Adult MSCs are derived from perivascular cells called pericytes. Pericytes can dissociate from the basal lamina of a blood vessel becoming exposed to the chemotactic environment of the surrounding tissue and transform into an MSC.[96] The Mesenchymal and Tissue Stem Cell Committee of the International Society for Cellular Therapy proposed a more formal definition that characterizes MSCs as cells with a thin and

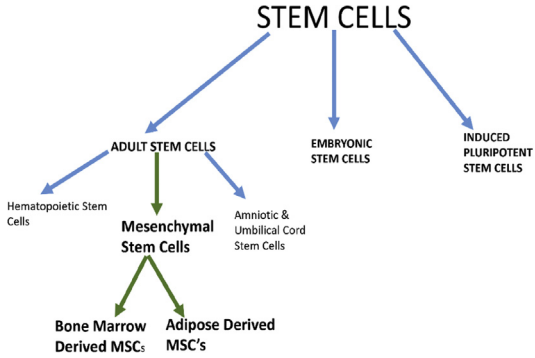

Fig. 3. Stem cell lineage. MSCs, mesenchymal stems cells. *Courtesy of* Prathap Jayaram, MD, Baylor College of Medicine, University of Texas Health Science Center, Houston, TX.

elongated morphology that can express specific surface markers and can adhere to plastic. They must also be antiinflammatory, antiapoptotic, antifibrotic, and possess immunomodulatory effects. The criteria further defines an MSC to have ability to self-replicate and differentiate into multiple cell types of mesenchymal origin.[97]

Sources

There are multiple sources of MSCs; bone marrow and adipose tissues are the current sources used in injectable orthopedic practice. The posterior superior iliac spine is the most commonly accessed landmark for bone marrow aspiration. Bone marrow aspiration is also known as bone marrow concentrate (BMC). This source provides cells containing MSCs, hematopoietic stem cells, endothelial progenitor cells, plasma, and a variety of soluble bioactive substances. Bone marrow cells can be further characterized into nucleated and nonnucleated cells. White blood cells and their precursors account for most of the nucleated cell fraction with red blood cells and megakaryocytes accounting for a smaller ratio of nucleated cells. Bone marrow MSCs (BMSCs) and hematopoietic stem cells account for an even smaller portion of nucleated cells averaging 1 in 10,000 to 1 in 50,000 of total nucleated cells. It has also been demonstrated that BMSCs viability and number are reduced by age and disease.[98] Adipose-derived MSCs are isolated from the stromal vascular fraction of homogenized adipose tissue. Adipose-derived MSCs, like BMSCs, are derived from pericytes. Compared with BMSCs, adipose-derived MSCs have a higher density per unit volume of tissue and able to proliferate in culture more quickly.[99,100] Despite these differences, there is no current evidence from clinical trials comparing adipose-derived MSCs and BMSCs for musculoskeletal injury.

Another potential regenerative injectable that has fallen out of favor clinically are amniotic tissue injections. Amniotic membrane–based products have various therapeutic applications in the foot and ankle, including the treatment of chronic wounds, fasciitis, and tendonitis. Although it is true that amniotic fluid does contain an abundant source of stem cells, the US Food and Drug Administration has only approved a form of amniotic tissue that after processing does not contain any live cells also known as dehydrated human amnion or chorion membrane.[101]

Clinical applications

Bone marrow concentrate injectables There has been an increase in clinical usefulness of using BMC injection treatment for articular cartilage defects, a common pathology affecting the elderly. Goldring and colleagues[102] demonstrated benefit of

this strategy at 24 weeks after percutaneous injection into the affected knee joint, showing a significant increase in cartilage and meniscus volume on MRI. Patients also attained increase range of motion and decreased pain scores. In a recent multicenter analysis of 2372 patients who underwent stem cell injections with a follow-up of 2.2 years, a total of 325 adverse events were reported.[1] There were 7 cases of neoplasm, lower rate than in the general population with lowest rate of adverse events observed in patients receiving BMC alone, compared with BMC plus adipose and cultured cells. Sampson and colleagues[103] have reported preliminary data that was targeted cartilage defects. They showed favorable outcomes in 125 patients receiving hip, knee, shoulder, ankle, or cervical zygapophyseal joint BMC injections. There was a 71% reduction in overall pain at a median follow-up of 148 days after injection in patients. Knee injections had the greatest improvement in pain scores compared with the other joints. Satisfaction with the procedure was reported by 92% of patients, and 95% would recommend the procedure to a friend.[103,104] These studies do support the safety profile of autologous BMC therapy for articular cartilage defects, with some evidence to suggest clinical efficacy.

Although there are numerous preclinical studies on MSC therapy in spine pathology, there are few clinical studies that have examined its efficacy. Pettine and colleagues[105] examined 26 patients (11 male, 15 female, aged 18–61 years, 13 single level, 13 two level) with chronic discogenic low back pain who received BMC injections into the disc. They were able to demonstrate beneficial effects with no disc worsening on MRI, and 21 of 24 avoided surgery for 2 years with improvements in functional outcomes and pain. There are 3 other studies with smaller numbers that demonstrate strong safety profiles and have shown beneficial subjective outcomes.[106–108]

As mentioned, tendinopathy is highly prevalent in the elderly. Rotator cuff tendinopathy in particular has a significant impact on upper extremity function. Hernigou and colleagues[109] examined 90 patients 10 years after routine arthroscopy, comparing those who did and di not receive BMC injections, and found 87% of patients had intact rotator cuffs compared with 44% in the control group, suggesting that MSCs here could have enhanced recovery and/or preventing further tendon degradation.

BMC therapy has shown an excellent safety profile in current applications to orthopedic injuries and there continues to be evidence to support this; however, the challenge of understanding the regenerative mechanisms at play is still not understood fully. Now that it has been established that BMC therapy is safe, more precision based studies that incorporate dosing profiles and standardizing pathology need to be done to better delineate regenerative mechanisms. Although long-term follow-up is essential, it is equally important to standardize MSC treatments to evaluate their outcomes more critically.

Adipose-derived concentrate injectables Adipose-derived MSCs have also been used in clinical practice with a good safety profile. Koh and Choi[108] performed MSC injections derived from adipose with arthroscopic lavage in elderly patients with knee OA. At the 2-year follow-up, 14 of the 16 patients showed improved or maintained cartilage.[108] Subjective functional outcome scores, the Knee Injury Osteoarthritis Outcome, visual analog scale, and Lysholm scores also improved with statistical significance. In a smaller study of 18 patients with intraarticular knee cartilage defects, Jo and colleagues were able to show decrease in cartilage defect size, improved knee function and decreased pain after injection

of adipose-derived MSCs.[109] Whereas adipose-derived MSCs have started to make more of a presence in injectable musculoskeletal strategies, more comprehensive studies need to be done to better understand the regenerative mechanisms.

Clinical indications, research, and future directions Exercise and activity in general are considered to be beneficial to health throughout life. As one ages, there are changes to the musculoskeletal system that are the result of attrition, overuse, and accumulated trauma. As a result, there is a cost to being active that is more prevalent and substantial in the older adult than in the younger adult. Musculoskeletal care will play a pivotal and continued role in the management of these conditions in the aging and active geriatric adults. There are promising therapies and emerging therapies that can help to manage and perhaps even reverse some of these changes. The use of tenotomy for tendinopathy has been demonstrated to be effective. Combining this treatment with biologic therapies such as PRP and prolotherapy may lead to more regenerative effects in tendinopathy. Stem cell treatment, although still not fully understood, is promising for tendinopathy and OA. Additional regenerative therapies, such as lipoaspirate and amniotic tissue–derived injectants with and without hyaluronic acid hold promise, and are now approved by the US Food and Drug Administration, but still poorly understood and lacking substantial evidence. Research should be focused on structural and physiologic effects of regenerative treatments and also in the clinical outcomes measured against conventional therapy.

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