Systematic Review

Exploring the Application of Stem Cells in Tendon Repair and Regeneration

Zafar Ahmad, B.Sc., M.B.B.S., M.R.C.S., John Wardale, Ph.D., Roger Brooks, Ph.D., Fran Henson, Ph.D., Ali Noorani, B.Sc., F.R.C.S., and Neil Rushton, M.D., F.R.C.S.

Purpose: To conduct a systematic review of the current evidence for the effects of stem cells on tendon healing in preclinical studies and human studies. **Methods:** A systematic search of the PubMed, CINAHL (Cumulative Index to Nursing and Allied Health Literature), Cochrane, and Embase databases was performed for stem cells and tendons with their associated terminology. Data validity was assessed, and data were collected on the outcomes of trials. **Results:** A total of 27 preclinical studies and 5 clinical studies met the inclusion criteria. Preclinical studies have shown that stem cells are able to survive and differentiate into tendon cells when placed into a new tendon environment, leading to regeneration and biomechanical benefit to the tendon. Studies have been reported showing that stem cell therapy can be enhanced by molecular signaling adjunct, mechanical stimulation of cells, and the use of augmentation delivery devices. Studies have also shown alternatives to the standard method of bone marrow–derived mesenchymal stem cell therapy. Of the 5 human studies, only 1 was a randomized controlled trial, which showed that skin-derived tendon cells had a greater clinical benefit than autologous plasma. One cohort study showed the benefit of stem cells in rotator cuff tears and another in lateral epicondylitis. Two of the human studies showed how stem cells were successfully extracted from the humerus and, when tagged with insulin, became tendon cells. **Conclusions:** The current evidence shows that stem cells can have a positive effect on tendon healing. This is most likely because stem cells have regeneration potential, producing tissue that is similar to the preinjury state, but the results can be variable. The use of adjuncts such as molecular signaling, mechanical stimulation, and augmentation devices can potentially enhance stem cell therapy. Initial clinical trials are promising, with adjuncts for stem cell therapy in development. **Level of Evidence:** Level IV, systematic review of Level II-IV studies.

Tendon injuries in the United Kingdom are a common problem. In 2009 over 30,000 hospital presentations were related to tendon injury.[1] Tendon injuries range from acute traumatic ruptures to chronic tendinopathy. Despite the improvements in conventional treatment such as surgery, clinical outcomes in tendon treatment are still variable. For example, massive rotator cuff repair can have a failure rate of up to 90%.[2] This has been largely attributed to tendon degeneration.

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The healing in injured tendon tissue in most cases results in formation of poor-quality tissue such as scar tissue, fatty infiltration, and matrix disorganization.[3-5] This results in degenerative tendon tissue that can develop over many years. Therefore it is not surprising that the surgical repair of this type of tissue can lead to high failure rates. Developments in surgical techniques include the use of allograft in repairs; however, this can lead to immune response and rejection.[6,7] Although the use of autografts avoids this problem, the disadvantage of this method is donor-site morbidity.[8] Therefore new strategies need to be devised to overcome this, such as tissue engineering techniques.

Tissue engineering, although officially defined in 1988, has been under development for many years.[9] The aim of tissue engineering in tendons is to generate high-quality tissue. One method that has produced much excitement is the use of stem cell therapy. The aim is to isolate a patient's population of stem cells and convert them into functional tendon tissue. This would avoid the immune reaction and donor-site morbidity associated with tendon grafting.

Tendon healing can be divided into 3 stages.[10] First, there is an inflammatory stage that involves the formation of a hematoma, the infiltration of white blood cells, and the release of cytokines and growth factors. Fibroblasts begin to appear in this stage, and macrophages will remove any debris. The second stage involves proliferation, where fibroblasts are producing mostly type III collagen and there is formation of new blood vessels. The final stage is one of maturation, where the collagens are cross-linked and the tissue becomes more organized. The tendon will achieve most of its original strength at 3 to 4 weeks and its maximum at 6 months.

Tendon heals with scar tissue, degenerating over time instead of regenerating normal tissue. There are several possible explanations for this. The first is that the tendon has a poor blood supply and therefore is not able to deliver optimal levels of growth factors and other nutrients necessary for regeneration. Other theories put forward include damage due to (1) repeated ischemia resulting from prolonged contraction, (2) free radicals resulting from reperfusion of the tendon after contraction, (3) hyperthermia from locomotion of the tendon, (4) microtrauma, and (5) inflammation. It is hoped that the delivery of stem cells will produce an environment that would be optimal for regeneration.

Our aim was to understand how stem cell therapy may benefit the area of tendon injuries. To achieve this, we performed a systematic review of the literature to identify the best available evidence on stem cells and tendon ail-

ments. Our primary hypothesis was that the addition of stem cells would improve tendon healing.

METHODS

We performed a comprehensive search of the PubMed, Medline, Cochrane, CINAHL (Cumulative Index to Nursing and Allied Health Literature), and Embase databases using various combinations of the commercial names of each stem cell preparation and the following keywords over the years 1966-2011: tendon, rotator cuff, supraspinatus tendon, Achilles tendon, patellar tendon, jumpers knee, ACL, anterior cruciate ligament, plantar fasciopathy, flexor tendon, extensor tendon, lateral epicondylitis, tennis elbow, stem cell, differentiated cell, mesenchymal cell, BMSC, bone marrow, stromal cell, CFU-F, MSC, IPS, induced pluripotent stem cell, multipotent cell, pluripotent cell, and embryological cell. All articles relevant to the subject were retrieved, and their bibliographies were hand searched for further references in the context of biomaterials for tendon repair. A total of 1,623 citations were identified from initial electronic searches.

Eligibility Criteria

The search (Fig 1) was limited to articles published in peer-reviewed journals and the English language without date restrictions up to August 15, 2011. We removed repeats and excluded from our investigation case reports, literature reviews, abstract-only publications, and letters to editors. A total of 221 articles fulfilled the criteria.

Extraction of Data

Data were extracted from the eligible articles, and differences were resolved by discussion. The article must have helped directly answer the question originally defined. Each study was also reviewed for the quality of its methodology. A descriptive summary of the results is presented. A total of 32 articles were selected for this article (Tables 1 and 2).

RESULTS

Mesenchymal Stem Cells and Tendon Repair

Bone marrow stromal or mesenchymal stem cells (MSCs) can generate multiple cell lines including bone, cartilage, and fibrous connective tissue, such as tendon.[16] They are non-immunogenic, not expressing major histocompatibility class II and co-stimulatory molecules.[17] Therefore allogeneic transplantation of

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                    │  Pubmed, Medline, Cochrane, │
                    │  CINAHL, BMJ Clinical Evidence│
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                    │        Search Terms         │
                    │ Combination of these search terms: 'tendon',│
                    │ 'rotator cuff', 'supraspinatus tendon', 'tissue│
                    │          engineering'       │
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                    │ 'stem cells', 'pluripotent  │
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│ The articles were searched over the years 1966-2011. All articles relevant to the subject were retrieved, and their│
│ bibliographies hand searched for further references in the context of biomaterials for tendon repair. The search was│
│ limited to articles published in peer review journals and the English language. We excluded from our investigation│
│                literature reviews and letter to editors.                  │
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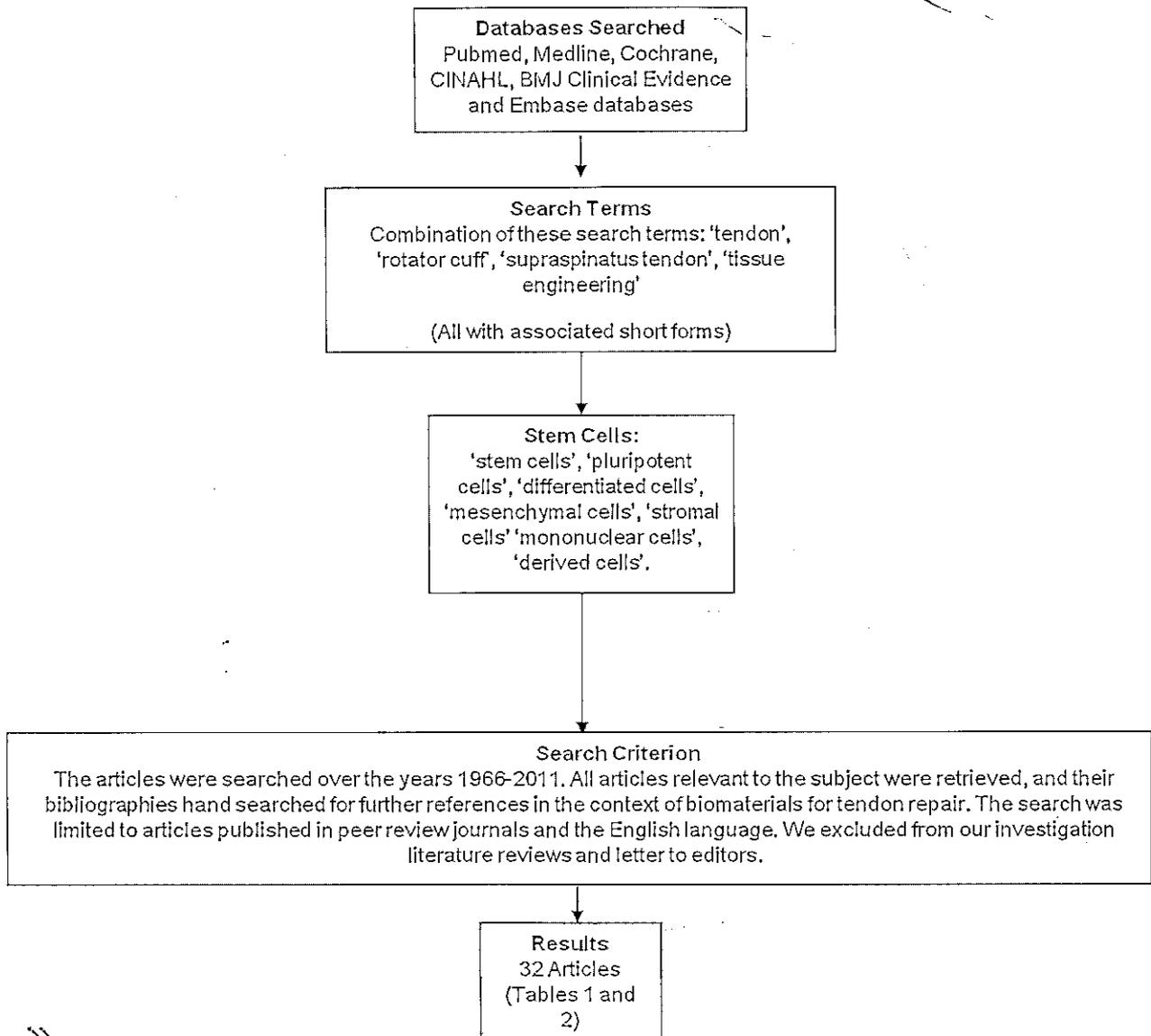
FIGURE 1.   Systematic review methodology for stem cells in tendons.

MSCs should not require immunosuppression of the host. In fact, MSCs themselves are immunosuppressive and suppress the proliferation of lymphocytes.[18]

Smith et al.[19] in 2003 found that injecting MSCs into a strain injury of 1 pony's superficial digital tendon improved the lameness but the ultrasound had shown no apparent increase in the substance or cross section of the tendon. Godwin et al.[20] found similar results when injecting 141 racehorses with tendon injuries. These outcomes can be explained by the results of the study of Watts et al.[21] in 2011, who randomized the injection of fetal-derived embryonic stem cells (ESCs) to 8 horses. Although there was no difference in collagen, DNA, or total proteoglycan between groups, the treatment group showed significantly improved tissue architecture, tendon size, tendon lesion size, and tendon linear pattern. Stem cells have also shown an effect on the density of collagen fibrils, as reported by Hankemeier et al.[22]

Stem cells have been shown to have a regenerative effect on tendon-bone healing. Nourissat et al.[23] repaired rat Achilles tendons in which the enthesis (bone-tendon junction) was destroyed, injecting chondrocytes, MSCs, or control. The MSC group showed

TABLE 1. *Results of Systematic Review of In Vivo Studies of Stem Cell Therapy*

Article	Stem Cell	Model	Method	Findings
Tendon repair				
Smith et al.[19]	BMSCs	1 pony—damaged superficial flexor tendon	Injection of stem cells 4 wk after injury; novel method of harvesting bone marrow	6 wk after treatment—lameness of pony improved; no increased thickening of tendon
Godwin et al.[20]	BMSCs	141 racehorses—overstrain injury of superficial digital flexor tendon; 2-yr follow-up	Intralesional MSC injection—cohort study	No adverse reaction was seen; reinjury rate was significantly less with MSCs compared with published data
Watts et al.[21]	ESCs 7	8 horses—superficial digital flexor tendon injury induced by collagenase	Randomized injection of fdESCs—1 wk after injury	Histology and ultrasound showed improved tendon lesion size and tendon size in fdESCs
Hankemeier et al.[22]	BMSCs	48 immunodeficient rats—surgical full-thickness window defect of tendon; 10 or 20 d follow-up	Human BMSC + fibrin, fibrin, or nothing (control) injected into defect	Experimental BMSC group showed dense collagen fibers, more cells, and less matrix
Nourissat et al.[23]	BMSCs	141 rats—Achilles tendon cut and enthesis destroyed; follow-up at 15, 30, and 45 d	All repaired surgically and then divided into 3 groups—control, chondrocyte injection, and MSC injection	Improved healing and load to failure found in injection groups; MSCs showed enthesis similar to native one
Lim et al.[24]	MSCs	48 rabbits—ACL reconstruction	Hamstring tendon coated with MSCs or control	At 8 wk, histologic analysis showed more similar interface with normal ACL-bone interface
Biomechanical benefit				
Awad et al.[25]	BMSCs	18 rabbits—surgical defect of right patellar tendon; 4 wk	MSCs applied in collagen gel in defect	MSC group showed significant increase in biomechanical strength but had little improvement in microstructure
Young et al.[27]	BMSCs	53 rabbits—surgical transection of Achilles tendon	Implants with MSCs or sutured (control)	Experimental group had greater load-related properties; collagen was more organized
Chong et al.[26]	BMSCs	57 rabbits—surgical transection of bilateral Achilles tendon; follow-up at 1, 3, 6, and 12 wk	Randomized—MSCs with fibrin or fibrin alone	Biomechanical and histologic parameters were stronger initially at 3 wk in experimental group, but at 12 wk, there was no difference
Ouyang et al.[28]	BMSCs	18 rabbits—hallucis longus tendons cut and translated into 2.5-mm bone tunnel in calcaneum; follow-up at 2, 4, and 6 wk	Treatment group had BMSCs	Histology showed that collagen fibers in experimental group were perpendicular whereas control group showed fibers along load axis

TABLE 1. *Continued*

Article	Stem Cell	Model	Method	Findings
Stem cell viability				
Ouyang et al.[30]	BMSCs	Rabbits—central-third patellar tendon defect; 8-wk follow-up	Implanted MSCs	MSCs had survived and differentiated from round to spindle shape
Guest et al.[31]	BMSCs	2 horses—superficial digital tendon; postmortem examinations performed after 10 or 34 d	Injection of MSCs—tagged	Labeled cells located mainly within injected lesions but with small proportion integrated into crimp pattern of adjacent healthy areas of tendon
Guest et al.[32]	ESCs or MSCs	8 horses—superficial digital tendon lesion (surgically created); up to 90-d follow-up	Injection of ESCs/MSCs after 1 wk after surgical operation	ESCs were shown to be high at 90 d, whereas <5% of MSCs survived
Dressler et al.[33]	BMSCs stored for 1 yr and 3 yr	27 rabbits—patellar tendon surgical defect	Implanted into defect in collagen gel	No difference in biomechanics between 1- and 3-yr-old groups (12 wk)
Enhancing stem cell				
Gulotta et al.[34]	BMSCs	98 rats—unilateral detachment and repair of supraspinatus	3 groups with (1) nothing (control), (2) fibrin carrier, or (3) MSCs with fibrin applied to repair site; follow-up at 2 and 4 wk	No difference in amount of cartilage or collagen fiber organization; no difference in biomechanical strength
Gulotta et al.[35]	BMSCs or adenoviral MT1-MMP (Ad-MT1-MMP)–transduced MSCs	60 rats—unilateral detachment of supraspinatus tendon and repair	3 groups—nothing (control), MSCs (fibrin glue carrier), or Ad-MT1-MMP	At 4 wk, Ad-MT1-MMP group had more fibrocartilage, higher ultimate-load-to-failure, higher ultimate stress to failure, and higher stiffness
Gulotta et al.[36]	BMSCs	60 rats—unilateral rotator cuff detachment; time points at 2 and 4 wk	2 groups—randomized; application in operation of MSCs in fibrin glue carrier or Ad-scleraxis–transduced MSCs	At 4 wk, scleraxis group had more fibrocartilage and was stronger mechanically
Schnabel et al.[37]	BMSCs or insulin-like growth factor I gene-enhanced MSCs (AdIGF-MSCs)	12 horses—bilateral superficial digital flexor tendon lesions induced by collagenase; follow-up at 2, 4, 6, and 8 wk	3 groups—treatment with MSCs, AdIGF-MSCs, or saline solution	Both MSC and AdIGF-MSC groups showed improved tendon histologic scores
Juncosa-Melvin et al.[40]	BMSCs	Rabbit—ex vivo model of surgical patellar tendon defect	Collagen sponge with MSCs	Mechanically stimulated increased collagen type I and III presentation
Butler et al.[9]	BMSCs	16 rabbits—surgical patellar tendon injury	2 groups—collagen-gel-sponge and collagen-sponge; half received mechanical stimulation; all received MSCs	Mechanically stimulated groups were significantly biomechanically stronger than nonstimulated group

TABLE 1. *Continued*

Article	Stem Cell	Model	Method	Findings
Omae et al.[11]	BMSCs with porous calcium hydroxyapatite ceramics	18 Japanese white rabbits—patellar tendon	Case control; follow-up at 3 and 6 wk	BMSCs had more bone formation and higher maximum pullout load
Vaquette et al.[45]	Poly(lactic-co-glycolic acid) knitted scaffold for tendon tissue engineering with MSCs	Rabbit—tendon	In vivo MSC group compared with no MSC control	After 13 wk, higher normalized elastic modulus, higher cell density, and vascularization compared with control
Yao et al.[43]	FiberWire suture (Arthrex, Naples, FL) with ESCs	Rabbit—Achilles tendon defect	Cohort study	Cells were shown to survive in affected area
Chen et al.[41]	MSCs impregnated with alginate beads	Rabbit—supraspinatus; 12 wk	Case control	No histologic significant difference between groups; however, more well-organized fibers and greater ultimate failure load were seen at 12 wk with MSCs
Alternatives to MSCs				
Nixon et al.[46]	ADNCs	8 horses—superficial digital flexor tendon injury induced by collagenase	4 horses treated with ADNC and 4 with saline solution injections	6 wk treatment—ultrasound saw no difference; histology showed a significant improvement in tendon fiber architecture, density, and reduction in inflammation in experimental group, but no differences in DNA and collagen content were found
Lee et al.[12]	BM-MSCs tagged with BMP-12	Rat—tendon defect	21 d; case control	Increased cell number elongation, alignment along tensile axis, greater matrix deposition, and elevated expression of tendon markers
Crovace et al.[54]	BMSCs or BMMCs	3 horses—collagenase-induced lesion	Treated with nothing (control), MSC injection, or BMMC injection	Histology showed normal architecture in tendons with MSCs and BMMCs, whereas control had scar tissue

Abbreviations: ACL, anterior cruciate ligament; Ad, adenovirus; Ad-IGF, adenoviral delivered insulin growth factor; BMP, bone morphogenetic protein; BMSC, bone marrow derived-mesenchymal cell or bone marrow stromal cell; ESC, embryonic stem cell; MT1-MMP, membrane type 1 matrix metalloproteinase.

an enthesis most similar to the premorbid state. Lim et al.[24] reported similar findings in rabbits undergoing anterior cruciate ligament repair.

Biomechanical Benefit of Stem Cells

Awad et al.[25] in 1999 conducted a case-control study of 18 rabbits over a period of 4 weeks in which the MSC group showed a significant improvement in biomechanics of repaired rabbit patellar tendons, but the microstructure of the tendon was not visibly improved. In a similar study of 53 rabbits, Chong et al.[26] found that repaired rabbit Achilles tendon treated with MSCs had greater load-related properties and reported better collagen organization at 3 weeks. The differ-

TABLE 2. *Results of Systematic Review of Human Studies of Stem Cell Therapy in Tendons*

Article	Stem Cell	Model	Method	Findings
Ellera Gomes et al.[13]	BMMC injection	14 patients with complete rotator cuff tears	Cohort study	At 12 mo, UCLA score improved from 12 to 21; MRI showed tendon integrity at 12 mo
Clarke et al.[14]	Skin-derived tenocyte-like cells	60 patellar tendons with tendinopathy in 46 patients	RCT	VISA score improvement from 44 to 75 in treatment group and 50 to 70 in control group
Connell et al.[15]	Skin-derived tenocyte-like cells	12 patients in area of lateral epicondylitis	Prospective clinical pilot study	Median PRTEE score decreased from 78 to 12 at 6 mo; 1 failure at 3 mo
Mazzocca et al.[58]	Bone marrow–derived MSCs	11 patients	Clinical investigation—cells were extracted and studied in laboratory	Produced connective tissue progenitor cells
Mazzocca et al.[57]	Human stem cells (connective tissue progenitor cells)	23 patients	Clinical investigation—cells were extracted and studied in laboratory	Tagged stem cells differentiated into tendon-like cells

Abbreviations: MRI, magnetic resonance imaging; PRTEE, Patient-Rated Tennis Elbow Evaluation; RCT, randomized controlled trial; UCLA, University of California, Los Angeles.

ence in the results can be explained because the study size of Chong et al. was significantly larger than that of Awad et al. Interestingly, Chong et al. found no biomechanical advantage at the 12-week time point of the study. This is contradicted by Young et al.,[27] who implanted MSCs into rabbit Achilles tendon repair sites. They found that the biomechanical advantage still existed at the 12-week time point. The difference in the results may possibly be because of the different delivery devices: Chong et al. used a fibrin carrier, whereas Young et al. used a suture laced with MSCs. We will discuss different delivery devices later.

The positive effects of stem cells on the biomechanics of tendon have also been shown by Ouyang et al.,[28] who conducted an experiment in which 18 rabbits had their hallucis longus tendons cut and translated into a 2.5-mm bone tunnel in the calcaneum. The histologic analysis showed that the group that received MSCs formed fibrocartilage at the tendon-bone interface. This has been found in previous studies to be consistent with increased biomechanical strength.[29] There was no formation of fibrocartilage in the control group.

Stem Cell Viability

One concern with stem cells is their ability to survive outside their native environment. Stem cells are taken from their native environment, cultivated and cultured in a laboratory, and then placed into tendon. This new environment may not be conducive in terms

of nutrition, blood supply, and growth factors to stem cell survival. Ouyang et al.[30] in 2004 showed the survival ability of MSCs by showing the persistence of tagged MSCs implanted into central-third patellar tendon defects in rabbits. These findings were corroborated by Guest et al.[31] in 2008, who injected labeled MSCs into mechanically created lesions in the superficial digital tendon of horses. Postmortem examination showed that the labeled MSCs were present in the lesion, surviving for at least 30 days.

Guest et al.[32] studied this further in 2010 by comparing the effects of MSCs with ESCs, injecting either into tendon defects of horses. The ESC levels were shown to be high even at the 90-day time point; in contrast, only less than 5% of the MSCs survived at 10 days. The ESCs showed an ability to migrate to other areas in the damaged tendon, whereas MSCs were detected only at the site where they were injected. The loss of the MSCs could be because of many reasons, including cell senescence or the serum used to prepare the cells. The short survival suggests that the MSCs may not be able to differentiate into tenocytes. However, the MSCs could exert their effect in other beneficial ways, such as reducing inflammation or releasing useful cytokines.

Stem cells have good viability in cell storage. Dressler et al.[33] in 2005 conducted a study in which MSCs were harvested from 27 rabbits at 1 year and 3 years of age and cryogenically stored. When the rabbits were aged 4 years, central-third patellar defects

were created, with either the 3- or 1-year-old MSCs being implanted at surgery. The results showed no difference in biomechanics, tendon cross-sectional area, or length between the 2 groups. This suggests that MSCs do not deteriorate with storage, and the study also shows that stem cells can be an "off-the-shelf" commodity, overcoming many of the difficulties of culturing MSCs. The limitation of this study is that there was a lack of control, so any healing benefit may be because of natural healing.

Enhancing Stem Cell Therapy

Need for Molecular Signaling in Stem Cells: Gulotta et al.[34] in 2009 conducted a case-control study of 80 rats that underwent unilateral detachment and repair of the supraspinatus tendon. MSCs were applied to the repair site and compared with a control with no applications. The outcome showed no differences between the groups in terms of the amount of fibrocartilage formation, collagen fiber organization, biomechanical strength of repair, and cross-sectional area of tendon. Gulotta et al. believed that the injured tissue may lack the signals to appropriately differentiate the transplanted cells.

Therefore in 2010 Gulotta et al.[35] conducted a similar study but used membrane type 1 matrix metalloproteinase, which is known to be upregulated in embryogenesis with the aim of driving the healing process toward regeneration rather than repair. The study showed that the membrane type 1 matrix metalloproteinase group had more fibrocartilage and stronger biomechanical strength compared with the control MSC group.

Gulotta et al. in 2011[36] further explored the idea of delivering signaling molecules with stem cells, by using scleraxis, again in a similar model. Scleraxis is a transcription factor that is thought to direct tendon redevelopment during embryogenesis. By transducing stem cells with scleraxis, the aim was to improve the healing of the tendon-bone structure. At 4 weeks, the MSC-scleraxis group had more fibrocartilage, as well as increased biomechanical strength, compared with the MSC control group.

The benefits of overexpressing signaling molecules in stem cells have also been shown by Schnabel et al.[37] in 2009, who showed that treatment of horse tendon lesions with MSCs and transduced MSCs both significantly improved histologic stores compared with the control, with the transduced MSC group having a higher biomechanical modulus than the MSC group. There was no difference between the groups in terms of DNA and collagen content, suggesting that

the MSCs did not persist or potentially reduced the inflammatory cell influx.

These series of studies show that there may be a need to have some control over the molecular signaling when delivering the stem cells. Stem cells by themselves may not be able to differentiate into the appropriate cell phenotype, and the injury site may not produce the correct signals. Therefore it may be that to achieve successful stem cell therapy, we need not only to be able to derive the current stem cells but to have the correct molecular signals as well—of which there may be several. However, these series of studies do show that there is much potential for stem cells in the repair of the rotator cuff.

Mechanical Stimulation Increases Type I and Type III Collagen Gene Expression: Juncosa-Melvin et al.[38,39] conducted studies in which they showed that mechanical stimulation preoperatively increases the stiffness of stem cell–collagen sponge constructs at 14 days in culture and in subsequent rabbit patellar tendon repairs at 12 weeks after surgery. They also showed that mechanical stimulation increases collagen types I and III gene expression of stem cell–collagen sponge constructs for patellar tendon repair.[40]

Butler et al.[9] conducted an experiment in which 16 rabbit patellar tendons were surgically injured and repaired. The groups were divided into (1) MSC–collagen sponge, (2) collagen sponge, (3) MSC–collagen sponge with mechanical stimulation, and (4) collagen sponge with mechanical stimulation. The collagen sponges were mechanically stimulated preoperatively. It was found that the mechanically stimulated group had significantly improved structural and material properties at 12 weeks. These studies have shown that preoperative mechanical stimulation of stem cell–collagen sponge constructs can enhance repair outcomes.

Augmentation Devices

Stem cells can be delivered directly or through augmentation devices. Augmentation grafts are being explored to deliver cells and bioactive molecules, including stem cells and various growth factors, to achieve tissue regeneration. A number of in vitro studies have shown successful delivery of stem cells through a scaffold with an improvement in tissue regeneration.[41-45] Chen et al.[41] found that surgically repairing the supraspinatus of rabbits with mesenchymal stem cell–impregnated alginate beads had a tendency to produce more well-organized tendon fibers,

with a higher ultimate failure load after 12 weeks. Vaquette et al.[45] found similar results when placing poly(lactic-co-glycolic acid) knitted scaffolds that were seeded with stem cells into rabbit tendons. After 13 weeks, they found that the tendons with stem cells had a higher cell density, had more vascularization, and were stronger biomechanically compared with naturally healed tendons.

Alternatives

There are a number of alternative sources for stem cells or cells similar to stem cells for tendon treatment apart from MSCs and fetal-derived stem cells.

Adipose-Derived Nucleated Cells: Adipose tissue can be harvested from several sites, such as the sternum or inguinal depots, and used to derive adipose-derived stem cells or adipose-derived nucleated cells (ADNCs). In horses treated with ADNCs, Nixon et al.[46] showed that there was a significant improvement in the tendon fiber architecture, reductions in inflammatory cell filtrate, and improvement in the tendon fiber density and alignment. This showed that ADNCs can improve tendon organization.

Induced Pluripotent Cells: Induced pluripotent stem cells (iPSs) are adult somatic cells "reprogrammed" to act as stem cells. Nagy et al.[47] induced pluripotent cells from the tendon fibroblasts in the equine model. The established iPS lines expressed pluripotency markers, displayed a stable karyotype even during long-term culture, and readily formed complex teratomas in an in vivo mouse model. The iPSs have the potential to develop a number of new regenerative therapies in veterinary medicine and provide a possible alternative for tendon stem cell therapy. Further studies will be needed to see what effects iPSs have on tendon injuries.

Tendon-Derived Stem Cells: Bi et al.[48] in 2007 showed the existence of tendon-derived stem cells (TDSCs). These are stem cells present in mature tendon that possess self-renewal and multilineage differentiation potential. TDSCs have the ability to differentiate into other cell types, such as muscle or fat cells.[49] These cells have been implicated as a possible cause of chronic tendinopathy because of the erroneous differentiation of TDSCs into abnormal matrix components causing fatty degeneration and calcification.[50,51] The main potential benefit of TDSCs is that they are resident cells in tendon. Therefore, when implanted into tendon defects, they are in an environment with which they are familiar and are likely to survive and differentiate into the correct cell type.

This area is still in the preclinical experimentation stage but has exciting potential for tendon therapy in the future.

Bone Marrow Mononucleated Cells: The extraction, culture, and delivery of MSCs comprise an expensive process. Blatt et al.[52] and Cho et al.[53] suggested bone marrow mononucleated cells (BMMCs) as an alternative. Crovace et al.[54] injected horses, tendon lesions with either MSCs or BMMCs and found normal architecture in the tendon in the treated groups and scar tissue in the control group. This study showed that BMMCs may be a possible alternative to MSCs.

Bone Marrow Aspirate Concentrate: Bidula et al.[55] showed that in the bone marrow aspirate of the iliac crest in humans, there are approximately 30 to 40 progenitor cells per 10^6 nucleated cells. Bone marrow aspirate concentrate methods have been developed by companies such as Harvest (Harvest Technologies Corporation, Plymouth, MA) and Thermogenesis (Thermogenesis Corporation, Rancho Cordova, CA). The aspirate is placed into a centrifugation machine, resulting in a concentrate 5 to 10 times the normal aspirate in minutes.[56] The product that results contains not only nucleated cells but other cells that could be potentially useful in regenerative healing, such as platelets. The advantage of this system is that the ease and quickness of production make it useful to employ during surgery. There are no published reports on this technology being used on tendons.

Clinical Trials

Connell et al.[15] in 2009 investigated the use of skin-derived tenocyte-like cells in the treatment of lateral epicondylitis. A total of 12 patients were injected with collagen-producing cells derived from dermal fibroblasts. Ultrasound and the Patient-Rated Tennis Elbow Evaluation scale were assessed over a period of 6 months at regular intervals. The median Patient-Rated Tennis Elbow Evaluation score decreased from 78 to 12 at 6 months, and decreases in tendon thickness, number of tears, and number of new vessels were seen. Of the 12 patients, 11 had satisfactory results; only 1 patient proceeded to surgery after failure of treatment at the end of 3 months.

Clarke et al.[14] in 2011 conducted a randomized controlled trial on 46 patients (60 patellar tendons) with patellar tendinopathy for injection with skin-derived tenocyte-like cells cultured in plasma. The control group was injected with autologous plasma alone. The Victorian Institute of Sports Assessment

(VISA) score and ultrasound were used to assess patients at 6 months. The results of the study showed an improvement in the VISA score in the treatment group from 44 ± 15 to 75 ± 17 at 6 months, as compared with 50 ± 18 to 70 ± 14 in the control group. The VISA score difference was significant. The patients who underwent cell therapy had faster recovery, and histopathology showed a normal tendon structure. Ultrasound appearances in both groups showed a significant decrease in hypoechogenecity and intrasubstance tear size. A decrease in tendon thickness was noted in the cell therapy group.

Mazzocca et al.[57] conducted an experiment to extract stem cells from the humerus during rotator cuff repair. Twenty-three patients were selected, and their bone marrow aspirates taken. These were then cultured by novel techniques. They were able to produce connective tissue progenitor cells, which have the potential of being used in future operations. In another study Mazzocca et al.[58] were able to show that bone marrow–derived stem cells differentiate into tendon-like cells when tagged with insulin. This group has shown that it is possible to extract, culture, and differentiate stem cells into tendon cells in humans.

In 2011 Ellera Gomes et al.[13] investigated the effects of BMMCs in 14 patients with complete rotator cuff tears. BMMCs were extracted from the iliac crest and injected into tendon borders after being fixed down by transosseous stitches. Each patient was assessed postoperatively with the University of California, Los Angeles score and magnetic resonance imaging. The findings at 12 months showed an improvement in University of California, Los Angeles score from 12 to 31, and magnetic resonance imaging showed tendon integrity in all 14 patients. Only 1 patient in the following year relapsed with loss of strength and pain. These results suggest that BMMC therapy is a safe treatment that has potential to enhance tendon repair.

DISCUSSION

We have summarized publications detailing the in vitro, in vivo, and clinical findings of stem cell therapy in tendons. This has shown that stem cells in tendons can increase collagen fiber density, enhance tissue architecture, and restore a nearly normal tendon-bone interface. Studies have shown that the biomechanical benefit of stem cells can be seen if the study is followed up over a longer period. Stem cells have been shown to increase the presence of fibrocartilage at the defect site. This has been shown to be associated with increased biomechanical strength. Stem cells are able to survive when extracted and placed into the tendon environment. They can also be stored for later use. The evidence presented in these articles shows that stem cells have the potential to stimulate events that can lead to regeneration.

However, there are still a number of challenges that need to be overcome before the full potential of stem cells can be realized. We believe that stem cells need adjuncts to be most effective. It has been shown that linking of stem cells with a molecular signaling molecule helps to differentiate stem cells into the correct cell types. This molecular signaling is involved in guiding the stem cell in tissue regeneration, maintenance, and repair. However, this area is not clearly understood at present. Further investigation is needed to determine what the most effective molecular signals are, as well as how they regulate the fate of stem cells in normal and injured tendons.

We have also shown that prior mechanical stimulation increases the expression of collagen at the defect site. This has yet to be explored in a clinical trial. Although the expression of collagen is increased, this has yet to be shown to translate into any clinical or biomechanical advantage.

There are a number of possible sources of stem cells for tendon and tendon-bone junction repair, including adipose-derived, skin-derived, and bone marrow aspirate concentrate. The advantage with some of these cells is that they are relatively easy to obtain and use in a clinical environment. More studies are required to understand the healing outcome and fate of these different sources of cells when implanted in different clinical models.

Tendon tissue that is torn is often degenerative, frayed, and retracted, and the surgical repair of this tissue is frequently subject to failure.[59] Stem cells offer the option of regenerating the tendon tissue and can produce a stronger tendon repair construct. There are several clinical options that have been explored that could potentially be applied in clinical practice.

The available evidence for the use of stem cells in tendons is limited. Preclinical studies are only just exploring the use of adjuncts such as molecular signaling to enhance stem cell therapy. There are, at the moment, 5 clinical studies, of which only 1 is a randomized controlled trial and 2 are cohort studies. These studies have small numbers of patients; however, all studies have shown positive outcomes in humans.

CONCLUSIONS

The current evidence shows that stem cells can have a positive effect on tendon healing. This is most likely because stem cells have regeneration potential, producing tissue that is similar to the preinjury state, but the results can be variable. The use of adjuncts such as molecular signaling, mechanical stimulation, and augmentation devices can potentially enhance stem cell therapy. Initial clinical trials are promising, with adjuncts for stem cell therapy in development.

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Technical Note

Area-Based Determination of Bone Loss Using the Glenoid Arc Angle

Guillaume D. Dumont, M.D., Robert D. Russell, M.D.,
Michael G. Browne, M.D., and William J. Robertson, M.D.

Abstract: In patients with anterior glenohumeral instability, the most commonly observed osseous defect involves the anterior portion of the inferior glenoid. The amount of glenoid bone loss guides surgical treatment, with progressively larger defects not being amenable to arthroscopic soft-tissue procedures. Currently, there is no universally accepted method of quantifying glenoid bone loss. Two-dimensional area-based methods and 1-dimensional methods of measuring bone loss have both been described but cannot be used interchangeably. The surface area of a glenoid bony defect is a more comprehensive descriptor of its magnitude than the 1-dimensional width of the defect. Calculating surface area can be challenging. We describe a method of quantifying glenoid bone loss using a glenoid arc angle that corresponds to the surface area of the defect. The arc angle is easily measured by use of commonly used imaging software tools and is independent of the size of the glenoid or defect orientation. This method may prove valuable in preoperative planning for patients with anterior glenohumeral instability.

The glenohumeral joint is inherently predisposed to instability by its bony architecture. The incidence of traumatic shoulder instability is 1.7% in the general population.[1] Factors that should be considered in determining the treatment of choice in patients with anterior glenohumeral instability include patient age, gender, activity level, and sports participation.[2,3] Perhaps one of the most significant factors in determining the surgical procedure of choice is the degree of glenoid bone loss.[4] Bony injury to the anterior glenoid rim, in the form of either a bony Bankart lesion or attritional bone loss, is common in patients with glenohumeral instability and can contribute to recurrent glenohumeral instability.[5] Patients with increased severity of glenoid bone loss treated with arthroscopic Bankart repair are at higher risk for recurrent instability.[4,6-8] These patients may benefit from surgical treatment such as open soft-tissue stabilization procedures or bony reconstruction procedures. In patients with significant anterior glenoid bone loss, the Latarjet procedure, which involves transfer of the coracoid to the anterior glenoid usually through a slit in the subscapularis, has shown decreased rates of recurrent instability when compared with arthroscopic Bankart repairs.[9]

Given treatment options including nonoperative management, arthroscopic stabilization, and open stabilization with bony augmentation, it is important to be able to accurately quantify glenoid bone loss to determine the appropriate treatment plan. Although much attention has been focused on the importance of