Regenerative Approaches to Tendon and Ligament Conditions

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KEYWORDS

• Soft tissue injuries • Tendon and ligament injuries • Stem cell therapies
• Regenerative medicine

KEY POINTS

- Healing of soft tissue injuries and lesions are often incomplete leaving the patient with residual pain, joint dysfunction, and functional disabilities.
- There are multiple types of platelet preparations which need to be properly selected depending on phases of healing.
- Stem cells derived from multiple sources may help modulate tissue repair.
- Extracellular matrix proteins and scaffolding may help facilitate tissue remodeling by providing a mechanical and biological environment for cells to migrate into, align and proliferate.
- Growth factors modulate tissue repair.

INTRODUCTION

Soft tissue pathology caused by acute injury, cumulative stress, or the sequelae of biomechanical faults and degenerative changes represent a significant portion of the practice of physical medicine and rehabilitation and sports medicine physicians. For many years, nonoperative management choices included rest, physical therapy, splinting and orthosis, medications, and physical modalities that often left patients with few other options for management of soft tissue injury. Healing of soft tissue injuries and lesions is often incomplete, leaving the patient with residual pain, joint dysfunction, and functional disabilities. Patients and physicians who

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Phys Med Rehabil Clin N Am 27 (2016) 941–984
http://dx.doi.org/10.1016/j.pmr.2016.07.003 **pmr.theclinics.com**

manage these conditions are left searching for treatment options and alternatives. Intratendinous injections of corticosteroid may reduce stiffness and pain but also reduce the physical forces required to injury the tendon in the future.[1–3] Injury to ligaments often results in joint effusion, altered movement, muscle weakness, reduced functional performance, and may result in significant loss of time out of play.[4]

Over the past 2 decades, technological advancements are emerging that use a "tissue engineering" approach to these conditions. Langer and Vacanti[5] first described 4 basic components required in tissue engineering: a structural scaffold, a cell source, biological modulators, and mechanical modulators. As various biologic and biocellular techniques have emerged, physicians have been trying to make the translational application to clinical practice where various treatment protocols are being developed. Unfortunately, the empirical experience with these techniques far exceeds the validation of these techniques in controlled studies.

The anterior cruciate ligament (ACL) is of particular importance, with some unique features that warrant discussion. Worldwide, young athletes experiencing anterior cruciate ligament injuries range from 17% to 61%.[6] In the United States, 350, 000 ACL reconstructive surgeries are performed annually.[7] The ACL is thought to have a poor healing capacity with a substantially higher rate of failure, which has led to a unanimous abandonment of suture repair and adoption of ACL reconstruction as the goal standard of care for ACL injuries, especially in younger athletes, whose primary goal is to return back to high-level sports activity.[4] Because the ACL is an intra-articular, extrasynovial ligament, ACL injury and the disruption of the synovial sheath do not allow a local hematoma formation to take place, which is crucial for the onset of the inflammatory response that would stimulate primary healing.[8] Despite ACL reconstruction, those athletes who successfully return back to play are at high risk for a second injury[9] and will have a less favorable outcome.[10] Importantly, ACL injuries are associated with long-term clinical sequelae despite ACL reconstruction, such as meniscus tears, chondral lesions, and the onset of posttraumatic osteoarthritis.[11–16] Recent technological advancements in tissue engineering and regenerative medicine have demonstrated promising use of novel biologic/tissue engineering techniques that include growth factors, stem cells, and the use of bio-scaffolding to improve ACL healing and repair.[17]

Primary disorders of tendons (tendinopathy), due to overuse or age-related degeneration, are common problems encountered in the day-to-day practice. Although there are no accurate figures specifically related to tendon disorders, studies from primary care show 16% of the general population suffer from rotator cuff shoulder pain and 21% in the elderly.[18,19] The incidence of rotator cuff pain is even more common in the sports community. It has been stated that injuries to tendons are involved in 30% to 50% of all sports injuries.[20] Rotator cuff disease is the most common upper extremity disability.[21] Due to hypocellularity and hypovascularity in tendinopathy, the natural ability of tendons to heal is extremely low.[22]

As biocellular techniques and tissue engineering protocols continue to emerge, we will need a more comprehensive classification system based on ultrasonography and clinical presentation to identify which type of tissue engineering strategy would be most appropriate for the category of tendinopathy. Developing both diagnostic and interventional skills using high-resolution ultrasonography will become increasingly important as regenerative medicine and tissue engineering techniques and protocols continue to emerge. Sensitivity figures of 0.98 are reported when using a 10-MHz or greater frequency ultrasound probe when detecting full-thickness rotator cuff tears.[23]