Chapter 9
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Autologous Expanded Mesenchymal Stem Cell Implantation for Orthopedic Conditions as a Non-Surgical Approach: A Recent Study

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ABSTRACT

This article aims to address the best practice in regenerative medicine. In principle, we use autologous expanded mesenchymal stem cells (MSCs) combined with platelet-rich plasma (PRP) in orthopaedic conditions for cartilage and tendon repair as an alternative to surgical intervention. Osteoarthritis (OA) denotes an absolute and usual path for all major traumatic slurs to synovial joints. OA is the most common form of degenerative joint disease and a foremost source of pain and incapacity. Despite the worldwide rise in OA occurrence, there are no effective pharmacotherapies to restore impaired articular cartilage's unique structure and function. Tendon tears never heal naturally due to their poor blood supply, and currently, surgical repair is the only available option to repair symptomatic tears. Accordingly, cell-based, and biological therapies for OA and related orthopaedic conditions grow into flourishing areas of development and research. Autologous MSCs have been tried to manage osteoarthritis and other orthopaedic pathologies for the last two decades, but it remains experimental therapy.

Keywords: Mesenchymal stem cells; MSC; PRP; osteoarthritis; cartilage; tendon tear; repair.

1. BACKGROUND AND DISCUSSION

Osteoarthritis (OA) is the most common form of arthritis and holds marked unpredictability of disease manifestation. The disease onset is varied, and the sequence of joint involvement and disease progression differs between individuals. The frequent symptoms of OA are joint pain, stiffness, joint swelling, restriction of joint movement, and functional limitations. Later, it can also lead to muscle weakness and wasting, poor balance, and joint deformities. Symptoms usually present in just one or a few joints in a middle-aged or older person.

Tendon tear (TT) can be asymptomatic and discovered incidentally on routine imaging. They usually do not require any intervention. Sport and non-sport Injuries can contribute to TT; the tendon has limited ability to heal independently, and most often, surgical repair is recommended in people failing non-operative therapy. The recovery time after surgery can be a lengthy process.

Management of orthopaedic conditions generally uses a conservative approach with anti-inflammatory medication, physical therapy, and sometimes steroid injections for symptomatic relief and restore function. Those measures will not alter the outcome of the disease process.
We summarize our findings from various literature reviews and our experience using combined fat-derived expanded MSCs-PRP therapy in many hundreds of clients for OA and tendinopathy, namely TT.

There are three main questions: What is the combined MSCs-PRP therapy mechanism? Does it work? And is it safe?

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MSCs (Fig. 1) are multipotent cells with a regenerative ability via direct and indirect effects. The explicit incorporation into injured and adjacent tissue (i.e., cellular engraftment), while the indirect pathway is related to un-engrafted MSCs producing paracrine signals cytokines that contribute to tissue regeneration by promoting growth and differentiation of local cells [1]. MSCs have an anti-inflammatory effect, immune modulation, and anti-apoptosis (programmed cell death) effect. In addition, they can self-renew and differentiate into various cells like chondrocytes, tenocytes, or other cells, depending on where we implant them [2,3].

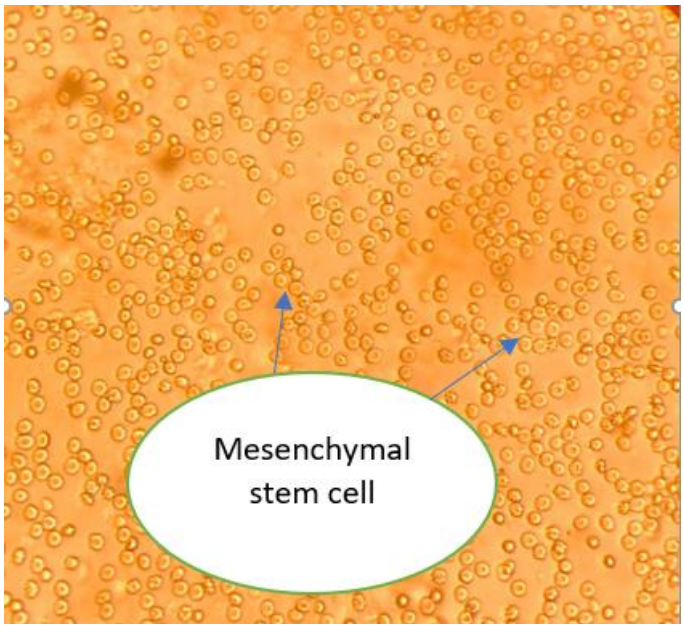

Fig. 1. Shows fat-derived mesenchymal stem cells before culture

Randomized and non-randomized clinical trials showed positive outcomes to the MSC therapy, particularly in knee OA [4]. In our practice, we found a success rate of an average of 70-80%, with best results for the knee involvement followed by the hip and shoulder OA; the good results are more seen in appropriately selected candidates with osteoarthritis "non-bone-on-bone pathology."

We based success rate on symptom control, quality of life improvement, slowing or stopping the radiologic progression of the disease, and eliminating the need for surgery at least in the first five years of its use. We might need to repeat the implantation in severe cases. This therapy is favoured over the surgery by speedy recovery, comfort in performing routine daily activities, quick return to work and sport. We noticed good effect varies starting from two weeks post-therapy for up to a year to see the maximum benefit. The excellent news with the expanded stem cell culture technique is that we can cryopreserve the MSCs in liquid nitrogen under -190° for up to 15 years or longer; this will allow us to repeat the implantation at the same place or implicate it in other areas.

While the degenerative process takes many years thus regeneration is also a slow process; therefore, we feel repeating imaging too early will not reveal the appropriate comparison. We have concluded MSC therapy stops or slows the progression of osteoarthritis and, on some occasions, recovers some of the cartilage thickness and other osteoarthritic pathologies. Still, those are inconsistent findings, and the process is slow [4,5].

PRP works by the activation of the platelets by the release of their intracellular cytoplasmic granules. Those particles contain inflammatory and growth factors which could be responsible for the healing process. The common ones are Platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), transforming growth factor (TGF)-beta, fibroblast growth factor (FGF), and epidermal growth factor (EGF) [6].

In our clinic, we have used various PRP preparation and techniques. Using a high PRP dose utilizing Anticoagulant Citrate Dextrose Solution-A (ACD-A) sterile tubes was the best outcome. We use no gel in our tubes to ensure good separation of the blood component (Fig. 2) in one session compared to multiple sessions, which have the disadvantage of exposing the patients to painful procedures, risk of complications like infections, and more costly. Furthermore, the addition of soluble hyaluronic acid has a potentiation effect on plasma therapy, and we found leukocyte-poor plasma is effective and less painful during and after the injections.

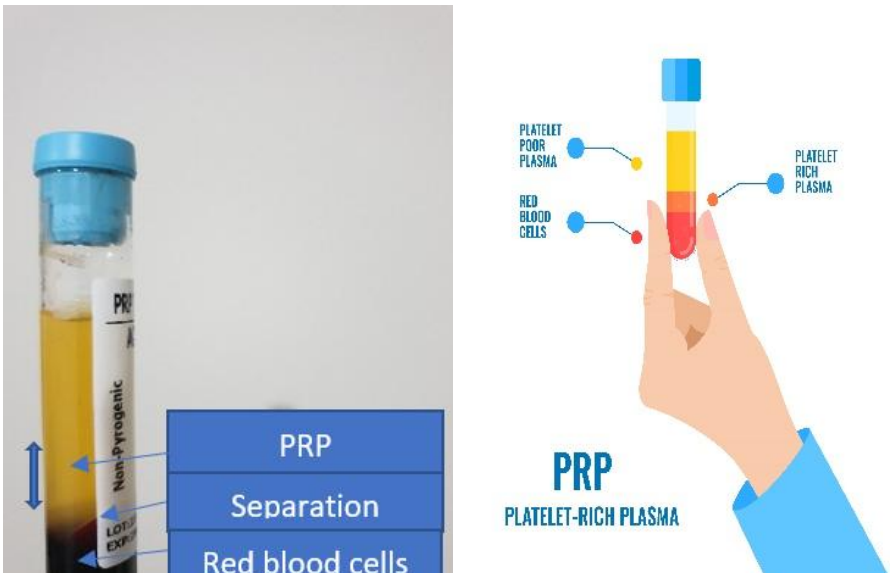

Fig. 2. demonstrates good plasm separation

The main obstacle with cartilage regeneration is the lack of direct blood supply, but instead, cartilage takes its blood source from the subchondral bone and nutrients from synovial fluid. Modified scaffolding techniques like exosomes and hyaluronic acid (HA) have potentiated effects on stem cell therapy.

HA has viscous-supplementation physiologic and anti-inflammatory, anti-oxidative, and immune-regulatory pharmacologic positive effects in OA [7]. We believe any scaffold (s) with anabolic effect including PRP, HA, exosomes, and non-synthetic collagen would add substantial synergistic and anabolic benefits to the MSC therapy.

Exosomes are micro-RNA particles released by all cell types and are found in large quantities in body fluids, including blood, saliva, urine, and breast milk. Exosomes work like biologic garbage bins that carry lipids, proteins, mRNAs, non-coding RNAs, and even DNA out of cells [8]. Exosomes enhance cell-cell communication [9]. We found autologous plasma exosome therapy (Fig. 3) is more effective than fat-derived ones. We have tried exosome therapy combined with MSCs in joint and tendon pathologies in several patients, and we found good clinical outcomes. We have been attempting the exosome therapy to be injected following the implantation of the mixture of MSCs and PRP but not in the same syringe to avoid unfavourable chemical effects, namely gel formation.

Cell culture is an essential practice in the fields of biology and medicine. It involves isolating cells from natural tissues, simulating the survival environment *in vivo* to ensure their growth and reproduction, and preserving their primary structures and functions under sterile conditions with proper temperature, pH, and suitable nutrient conditions [10]. This is three-dimensional (3D), more advanced than the traditional 2D cell culture (Fig. 4), as we are trying to mimic the internal structures like cartilage, tendon, muscle, bone, and others.

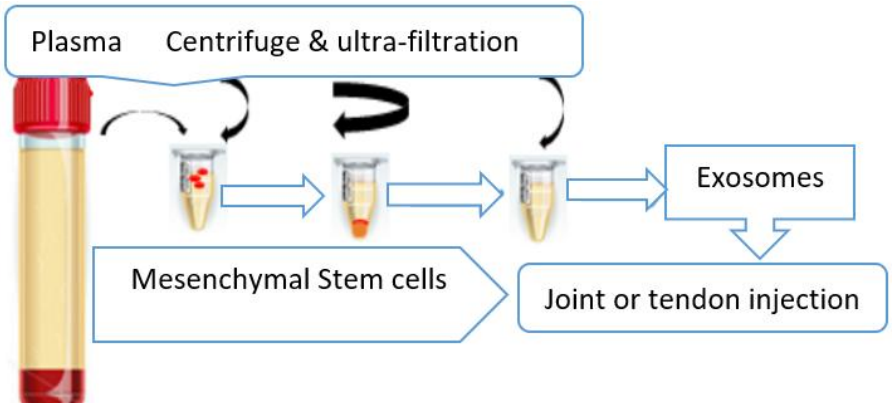

Fig. 3. Shows the extraction of plasma exosome to potentiate the stem cell therapy

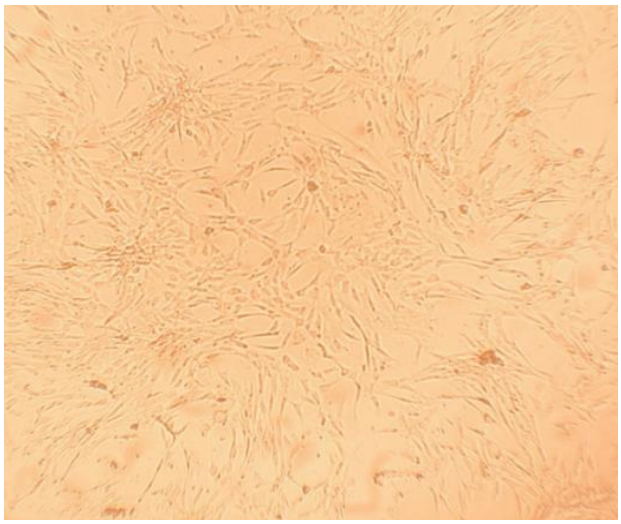

Fig. 4. Shows standard 2D culture with stem cell actively growing -60% confluent

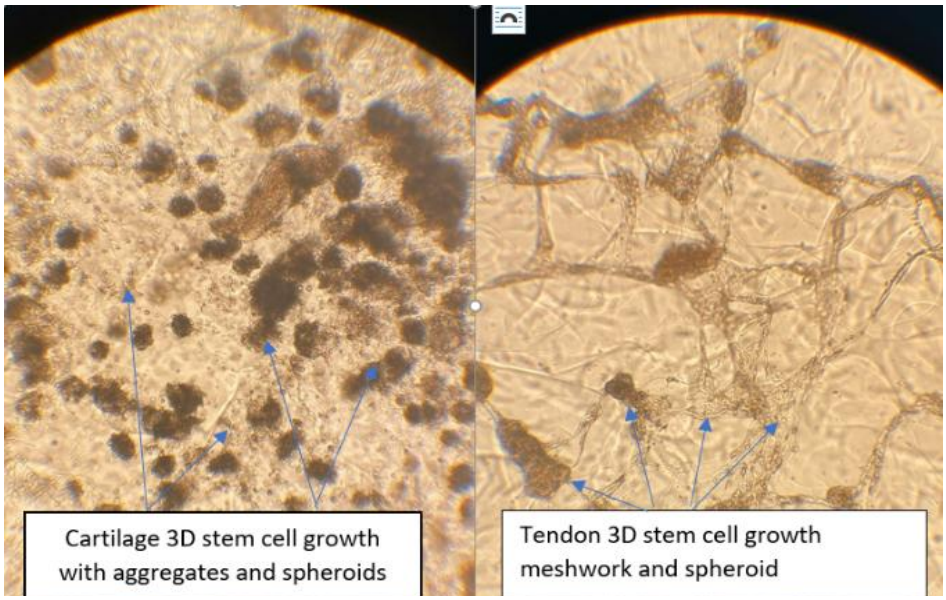

Fig. 5 shows 3D cell culture

We have tried FDA-approved human-compatible bovine collagen type1-hyaluronic acid in 3D stem cell culture (Fig. 5). We did not use any synthetic materials for safety reasons, and we found a good clinical effect. In an anecdotal case report, the 3D cell culture technique has regenerated massive labral tears and resolved hip para-labral cysts; those findings have not been seen with any other medical therapy [11]. This was an open-labelled trial; thus, we believe a randomized-controlled practice is worth undertaking to compare it to the standard 2D technique.

In terms of tendons regeneration, we have found that the combined MSCs-PRP therapy is significantly effective in symptom control, substantially improves range of motion, and may eliminate the need for surgery [12,13,14,15]. The success rate is 80-90% of the cases in our practice. The clinical benefit was noticed even when there was no clear radiological evidence of tendon healing. We have observed MRI healing of rotator cuff tears and Achilles tendinopathy.

Some factors might affect the efficacy of MSCs-PRP therapy, including local anaesthesia use inside the joint or tendon injected due to its toxicity to both MSCs and platelets. Alcohol and non-steroidal anti-inflammatory medicine before and after the stem cell implantation can reduce its efficacy, while the use of turmeric/Boswellia as natural preparation help to reduce the inflammatory response post-implantations of the stem cells.

The safety of autologous MSCs is well tested in several clinical trials; it has shown no evidence of rejection given both the blood and the cell-based therapies are extracted from the same individual. There is no evidence of developing malignancies in autologous adult MSCs [16,17,18]. We avoid using MSCs-PRP in patients with active cancer or in remission with invasive cancer for at least five years from its onset to prevent overstimulation of the pre-existing cancer cells. Additionally, both PRP and MSCs have some antimicrobial activity [19,20]; thus, infection is infrequent, particularly we sterilize the expanded cells with both antibiotics and antifungal solutions. Also, we adapted single-use sterile PRP tubes.

Generally, the doses we use in large areas range between 50-100 million MSCs in 2 MLS of fluid combined with 5-8 MLS of PRP in the same syringe depending on the size of the area(s), but in smaller joints, we modify the number of cells and PRP volume. Additionally, we found that concentrated MSCs without PRP are more effective for small joints of the hands and feet [21]. The number of MSCs used in the expanded technique makes the therapy more effective than the low number used in the same-day procedure, i.e., the stromal vascular fraction (SVF); thus, expansion of MSCs is encouraged if the regulatory authority allows this practice. We have tried our therapy for all upper and lower limbs joints and tendons, including large and small areas. We did not use intravenous MSC therapy as we believe targeted local injections under ultrasound guidance are more relevant for the local repair of the affected tissues.

2. CONCLUSION

In summary, we believe this is future medicine. If used early in the disease process, it could replace surgery before developing bone-on-bone pathology or major tendon tears with significant retractions. However, more work and research are needed to advance and standardize the best protocol by choosing the correct number of MSCs used in each area and the PRP dose and centrifuge technique to ensure the maximum effective and safe doses.

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COMPETING INTERESTS

The author has declared that no competing interests exist.

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Biography of the author(s)

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The number of Published Papers: He has six research articles.

Special Award: He has Certificates of Appreciation (Best Award) video Talk and two Certificate of Recognition in Stem Cell Therapy at SciTech Genomics, Proteomics and Bioinformatics 2021, Certificate of recognition in World Congress on "Pain Research & Management" held during November 17-18, 2021.

Any Other Remarkable Point: Ultrasound-Guided Procedures in musculoskeletal conditions.

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