Australasian College of Sports Physicians—position statement: the place of mesenchymal stem/stromal cell therapies in sport and exercise medicine

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ABSTRACT

Purpose and scope This Position Statement has been written expressly for members of the Australasian College of Sports Physicians (ACSP); however, it may also be of interest to the wider medical community, sporting organisations, athletes and the general community. It has been informed by a comprehensive review of the scientific literature and the opinions of kindred organisations. This statement outlines the use of mesenchymal stem cell (MSC) therapies in the broad context of Sport and Exercise Medicine, recognising that every medical practitioner should respect: (1) the evidence for the therapeutic use of MSCs and (2) the priority for patient health and welfare.

INTRODUCTION

Mesenchymal stem cells

While many types of stem cell exist, they all possess two distinct properties. First, the ability to self-replicate (proliferate), and second, their potency or ability to differentiate (transform into mature adult tissue). Stem cells derived from and returned to the donor are termed ‘autologous’, while those administered to a non-tissue-matched recipient are referred to as ‘allogeneic’ stem cells.

Mesenchymal stem cells (MSCs) are derived from stromal tissue and described as multipotent, having the capacity to differentiate into mesodermal and endodermal types of cells, depending on the tissue matrix.1 Their multipotency, specific surface antigen expression and their plastic adherence properties when cultured are required for the definition of MSCs.2

This Position Statement only applies to MSC therapies and not to embryonic, haematopoietic or induced pluripotent stem cells; cellular therapies involving autologous tenocytes, autologous chondrocytes or platelet therapies.

Expanding MSC populations

MSCs can be extracted from adipose and synovial tissue, peripheral blood, skeletal muscle, umbilical cord blood, placenta, and bone marrow. Generating high numbers of MSCs requires several steps. First, harvesting, commonly from bone marrow or adipose tissue, then a stage of isolation and finally encouragement to proliferate. This MSC expansion process takes several weeks, is costly, highly technical but devoid of a ‘gold standard’. The resulting manufactured cells are called mesenchymal Stromal cells or mesenchymal progenitor cells. The MSC expansion processes result in variable cell populations with different cellular properties.3 The expanded cell populations also display reduced migration differentiation with consequences on their capacity for graft formation.4–8 The lack of standardisation between the commercially available MSC expansion protocols makes comparisons between products and studies relating to those products difficult.9

A contemporary development in manufacturing techniques employs far shorter preparation times (often less than 2 h) at far less cost, producing a non-expanded mixed cell population. However, MSC numbers are low in these preparations, and the presence of multiple cell types raises questions about the efficacy of these techniques.10 While the progress in biotechnology has resulted in commercially attractive outcomes, the science substantiating their effectiveness has lagged behind. This has been called an ‘unhealthy system’.11 No published randomised controlled trials for ‘same-day bone marrow stem cell concentrates’ are available as of 2015.12

MSCs and their therapeutic utility

MSCs secrete growth factors and cytokines with trophic, chemotactic and immunosuppressive properties.2,7,8,13,14 Experimental studies in animals show their potential for influencing musculoskeletal tissue regeneration and enhancement rather than fundamental repair, as would occur in simple scar formation.15–17 Therefore, MSCs have a potential regenerative influence on tissues damaged by repetitive overuse or through age-related degeneration. The pre-programming of MSCs to form a specific tissue has intriguing theoretical consequences for tissue regeneration and potential enhancement.

Given their low numbers, MSC populations for therapeutic use need to be expanded as outlined earlier. The ideal prerequisites for a satisfactory graft are large numbers of viable MSCs that do not age prematurely, and with the capacity to differentiate accurately into the correct cell type of the target site. Some consider that before clinical trials proceed it is important to determine that the success of the graft as the consequence of MSC activity rather than the paracrine effects of the grafted material.18 There are still many unresolved challenges to the therapeutic use of MSCs.19

Clinical trials and MSC therapies

There is no evidence in the contemporary literature of any MSC therapy for use in musculoskeletal conditions having successfully completed a full clinical trial in accordance with the steps mandated by the International Society for Stem Cell Research.20

This protocol strictly adheres to a four-phase model of clinical trial necessary for any novel therapeutic intervention. Consequently, current variants of MSC therapy advanced by clinicians throughout Australasia have limited scientific credibility, may not meet the requirements for evidence-based clinical practice nor satisfy the criteria for patient safety. The fundamental steps of the widely accepted clinical trial process include:

**Phase I:** Researchers test the safety and assess adverse effects of an intervention in a small cohort of participants.

**Phase II:** The intervention is administered to a larger group to assess efficacy and to further evaluate safety.

**Phase III:** The treatment is administered to large identified groups of participants to confirm effectiveness, monitor side effects, provide comparisons with commonly used treatments, and to collect information that will inform future safe treatment.

**Phase IV:** Postmarket surveillance is undertaken (after the introduction of the therapy to clinical practice) to assess any adverse effects associated with long-term use.

There have been a number of concerns raised about the use of MSCs in clinical practice in the absence of evidence of clinical efficacy. This paper will address the scientific and ethical concerns.

**SAFETY**

MSCs by definition have the ability to transform/differentiate into a limited number of mature cell types (multipotency), making them different from embryonic stem cells that have pluripotent differentiation potential. This makes MSCs a safer option. However, questions remain including:

- Do MSCs have a tumorigenic effect?
- What is the mechanism of action of the therapeutic effect?
- Is greater therapeutic effect associated with greater risk?
- Do MSCs stimulate currently dormant tumour cells within the recipient?

Before phase I research can start, often preclinical animal models are used to better understand safety and adverse effects of innovative biological therapies. Suitable models for comparison to humans may be available, but sometimes artificial biological models need to be developed to mimic human disease state to assess biological response.

Safety studies need to be rigorous in design including strong institutional framework of peer review in the development phase, stringent ethical approval, implementation and follow-up to predetermined measurable and clinically relevant end points.

A systematic review and meta-analysis (2012) of the intravenous use of MSCs in 321 patients with a diverse group of medical conditions, including Crohn’s disease, stroke, myocardial infarction and cardiomyopathy, found their use to be safe. However, there have been three subsequent case reports of similar interventions that describe significant side effects—ventricular fibrillation, pulmonary emboli and acute disseminated encephalomyelitis. Malignancy associated with pluripotent stem cells in preclinical studies is of concern. In the case of MSCs, quality evidence of the risk of malignant transformation in humans is lacking. There is a case report of transplanted autologous cells presumed to be MSCs, causing a tumour 8 years later. The literature continues to question the potential for stem cell use to unmask dormant malignancy. A study of bone marrow-derived stem cells cultured for 4 weeks showed two of five cultures formed sarcoma-like tumours in vitro. A 4-week culture time is longer than MSCs currently available from commercial techniques; however, their tumour-forming potential remains a concern. If research suggests that larger numbers of stem cells are required for efficacy, then techniques of in vitro culture deserve further investigation. Only then can their in vivo application be considered to have no potential for tumourogenesis.

To date, research into the safe use of MSCs has not demonstrated tumour-forming potential or other significant side effects in phases I and II musculoskeletal research. However, long-term safety cannot be assured. By way of example, agents later withdrawn for reasons of safety include the COX-2 Inhibitors Rofecoxib and Vioxx and Lumiracoxib (Prexige). Both were withdrawn from the Australasian market several years after their introduction due to significant morbidity and mortality not evident in phases I and II research but discovered through vigilant postmarketing research (phase IV) after thousands of patients had been treated.

**Safety in osteoarthritis**

A systematic review of the safety of autologous bone marrow-derived MSCs in the treatment of osteoarthritis reviewed 3039 articles and found eight articles that met their inclusion criteria. In total, 844 procedures were followed for a mean of 21 months. Increased pain and swelling after the injection were the only adverse events reported as being related to the stem cell product. Importantly, the authors concluded that it is safe to continue development of stem cell therapies provided there is ‘continuous caution for potential side effects.’

A phase I/II double-blind, randomised controlled trial of 59 patients injected postarthroscopic meniscal surgery showed no difference between minor and major side effects between the low dose (50×10⁶ cells), high dose (150×10⁶ cells) and control groups and no ectopic tissue formation. The MSCs were from bone marrow aspirates of unrelated donors (allografts).

A further study of 91 patients in whom 100 joints were injected with autologous adipose MSCs were followed for an average of 26 months. No tumours were reported. However, swelling of the injected joints was reported as a common, but self-limiting side effect.

Several small studies have used MSCs as an adjunct to surgical intervention for the treatment of osteochondral defects in the ankle and knee. A total of 101 patients received MSCs compared with 51 control patients who had surgery without MSCs. There were no reported differences in significant adverse effects between groups.

Three small phase I/II studies comparing high tibial osteotomy (n=66) with high tibial osteotomy plus MSCs (n=74) showed no significant side effects between groups after a 2-year follow-up. There are other studies involving orthopaedic intervention, where MSCs were used as an adjunct, without any reported significant side effects.

**Safety in tendinopathy**

Few studies have examined the treatment of tendinopathy in humans with MSCs. Two case series treating patellar tendinopathy and 30 patients with lateral epicondylitis with bone marrow-derived non-expanded MSCs followed for 3 years and 12 weeks, respectively, reported no significant adverse effects. Another small series of 14 patients who had bone marrow-derived non-expanded MSCs injected around the surgical repair margins of full thickness rotator cuff repairs followed for 12 months showed no adverse outcomes.
One pilot study reported using cultured human tenocytes in the treatment of tendinopathy without any adverse effects. However, the use of tenocytes is not within the scope of this report.

Safety in muscle injury

There are no data in the literature that address the safety of MSCs in human muscle injury. Questions have been raised about the possibility of heterotopic bone formation in injured muscle treated with MSCs.

Efficacy

There are promising studies that MSCs enhance tendon repair in rabbit, rat, and horse models. MSCs have been demonstrated both in vitro and in vivo to be able to differentiate into articular cartilage, thus suggesting they may be useful for treating articular cartilage injuries.

There is biological plausibility that MSCs should be therapeutically used in the management of osteoarthritis. Laboratory-based evidence demonstrates MSC-mediated catabolic and inflammatory effects that should be chondroprotective. Osteoarthritis differs from an osteochondral defect. The former is a dynamic process where mechanical stressors and catabolic processes overwhelm the joints capacity for repair, whereas the latter can be an acute injury or metabolic condition.

Adipose tissue offers a readily available source of MSCs; however, the underlying ethical values important to the everyday work of sports physicians are also pertinent when considering the use of MSCs for muscle healing. MSCs exist in skeletal muscle. Homoeostasis and healing/repair of muscle is complex. To date, no literature has examined autologous MSC use in muscle injury.

Efficacy in osteoarthritis

The most appropriate method to determine if an intervention has a placebo effect is to undertake a double-blind, placebo randomised controlled trial (level 2 evidence). To date, there are no published studies of this calibre. There are several small cohort studies where injected MSCs showed improved pain and functional scores. Some reported evidence of arthroscopic or radiographic improvements to the articular cartilage at follow-up. There are several small studies comparing MSCs to hyaluronic acid—one 7-10 days postarthroscopic debridement, the others not related to surgery. While the MSCs were better than hyaluronic acid in the surgical group and equivalent to hyaluronic acid in the non-surgical group, it is difficult to fully interpret these results due to the nature of the comparison groups. Arthroscopic debridement surgery has been shown to worsen patient outcomes in knee arthritis, and it remains unanswered whether hyaluronic acid is therapeutic. It is not known whether MSCs ameliorate the detrimental effect of surgery and allow more acceptable surgical outcomes. Likewise comparing MSCs to a treatment with unproven outcomes is challenging to interpret.

The Osteoarthritis Stem Cell Advanced Research Study (OSCARS) remains the only double-blind, randomised placebo-controlled trial using injected MSCs for knee osteoarthritis. It demonstrates no difference in efficacy between the treatment group (receiving non-expanded adipose derived MSCs) and those who had MSCs harvested but received a saline control injection at any point out to 12 months follow-up. Although published as a conference abstract, the full study remains unpublished in a peer-reviewed journal.

Efficacy in tendinopathy

While there are a large number of articles looking at animal tendinopathies, many use collagenase-induced injuries rather than the clinical scenario seen in humans of overuse or age-related tendon degeneration. Two studies examining the equine equivalent of Achilles tendinopathy demonstrated a decrease in tendon re-injury rates compared with historical veterinary data. Animal models suggest that MSCs alone have less efficacy without the presence of a biological ‘scaffold’ and/or growth factors. This would suggest that without the scaffold and cytokine influence, the MSC effect is predominantly paracrine rather than the MSCs themselves integrating into the repair.

Efficacy in muscle injury

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ETHICAL CONCERNS REGARDING MSC USE IN MUSCULOSKELETAL CONDITIONS

The underlying ethical values important to the everyday work of sports physicians are also pertinent when considering the use of MSCs for musculoskeletal conditions. Respect for patient autonomy while promoting benefit and avoiding harm, and acting in a fair and just manner are some of the important ethical concepts that can be used to usefully reflect on this relatively new area of work. New developments in healthcare have the potential to benefit many. However, patients can be harmed as a result of the introduction of new therapies with insufficient evidence to support their widespread use. Therefore, good quality research is needed to ensure that innovations are safe and efficacious prior to wider clinical use. A balance must be struck that allows for a level of innovation, yet ensures that patient safety is paramount through the use of robust research to ensure safety and efficacy.

MSC therapy is an area of collaboration between the medical profession, and commercial and non-commercial interdisciplinarity groups in an area where the science is preliminary, not all the evidence is in the public domain and the regulations are evolving. Other countries have developed regulations to protect the consumer, but adherence to those regulations have varied. On some occasions, clinicians have ignored practice constraints and others have exploited regulatory ‘loopholes’ allowing treatments to be marketed to the public bypassing standards for innovative therapies coming to market.
The use of autologous MOCs for the treatment of musculoskeletal conditions is currently unproven, and therefore has not yet been determined to be safe or efficacious for clinical use and there is a lack of credible long-term data to support clinical application. \(^{21} 114 115 118 119\) Some of the risks and burdens associated with MSC use are well recognised as they arise by virtue of their route of administration (including injection-site infection, and wrong-site administration). \(^{21} 112\) Other aspects of MSC use where there are, as yet, no clear treatment guidelines may pose risks and potential harms that are yet to be determined, including cell preparation, dose and frequency, \(^{12}\) and any long-term harms that may eventuate. \(^{23}\) There is, therefore, a need to protect the patient from known and as yet unknown harms arising from new and unproven interventions. Not only must we consider the potential harms to an individual patient or research participant, but harms to the integrity of the medical profession and erosion of public trust in medical research \(^{116}\) through the unchecked practices of some clinics undertaking MSC therapy. Yet demand exists for new treatments in musculoskeletal care, particularly where the patient has few clinical options remaining. \(^{91} 106 120\)

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Athletes and physically active members of the community seek rapid resolution of their musculoskeletal problems. Consequently, they may be willing to accept treatment options that have not been subjected to full clinical scrutiny, in an endeavour to obtain accelerated ‘return to play’. These factors place pressure on doctors to consider new therapies where options are limited, but they also potentially leave patients vulnerable to exploitation. \(^{74}\)

In recent years, there has been a proliferation of clinics offering, \(^{116}\) and sometimes actively marketing, MSCs for treatment of several musculoskeletal problems. Some clinics have overstated claims about the efficacy and safety of MSCs given the current knowledge. \(^{75} 115 116 119 121\) Concern has also been raised about the high cost of care, the potential conflicts of interest clinicians might have, and the claims made in advertising given the absence of proven therapeutic benefit. Calls have been made for this area to be more stringently regulated. \(^{21} 115 116\)

So far, research in this area has revolved around autologous MSCs. Where research moves towards MSC allografts, the ethical considerations are more complicated and attract regulations to protect patients. \(^{122}\)

There are also concerns that patients may travel outside of their home jurisdiction to receive MSC therapy where regulatory requirements are less rigorous. Australasian College of Sports Physicians (ACSP) members need to be cognisant of these concerns and to the pressures this activity may place on them. \(^{74} 101\)

**Advertising**

As stated earlier, patients seeking MSC therapy have frequently reached the end of conventional treatment options; this may leave them particularly vulnerable to exploitation through the use of unwarranted claims of efficacy beyond what is currently known, or through testimonials from celebrity patients. \(^{112} 116 123\)

In both Australia and New Zealand, there is a clear expectation that advertisements or claims made about treatment must meet particular expectations. The Medical Board of Australia Code of Conduct \(^{104}\) states that:

- Good medical practice involves:
  - 8.6.1 Making sure that any information you publish about your medical services is factual and verifiable.
  - 8.6.2 Making only justifiable claims about the quality or outcomes of your services in any information you provide to patients.

8.6.3 Not guaranteeing cures, exploiting patients’ vulnerability or fears about their future health, or raising unrealistic expectations.

8.6.4 Not offering inducements or using testimonials

The New Zealand Medical Council statement on advertising makes similar demands, requiring that claims about services are factual and verifiable, and that people are not encouraged to have unrealistic expectations. \(^{124}\) The New Zealand Medical Association Code of Ethics specifically states that testimonials and endorsements not be used. \(^{125}\)

**ACSP POSITION**

The position adopted by the ACSP promotes patient safety and autonomy, endeavours to reduce potential harm to the patient, provides a level of clarity in an area of uncertainty, and takes responsibility for the advancement of knowledge. \(^{101} 106 122\) The ACSP position protects patients and the profession in the absence of unequivocal evidence regarding effectiveness and safety of these techniques, and yet responds to a recognised need to actively contribute to the development of knowledge in this area. \(^{101} 125\) The ACSP believes that robust knowledge generation is vital to improving patient care. \(^{106}\)

The ACSP believes that any use of MSCs for musculoskeletal conditions must fit within either of the following pathways:

1. As part of a rigorous clinical research trial.
2. As an individualised innovative therapy where there is a commitment to the transparent collection of data for analysis by a research body external to the clinic.

**As part of a rigorous clinical research trial**

The ACSP encourages the establishment of research studies to determine the safety and efficacy of MSC for the treatment of musculoskeletal conditions. MSC use for musculoskeletal conditions as part of a clinical research trial must be registered with an appropriate national or international clinical research trial registry. \(^{107} 114 127 128\) Any research trial must be subject to rigorous and independent scientific peer review prior to start of the study, and receive ethical approval from an accredited human research ethics committee. \(^{106} 107 129\) It is expected that any and all research findings are shared within the scientific and medical community including adverse outcomes. \(^{106} 112 129\)

**As an individualised innovative therapy where there is a commitment to the transparent collection of data for analysis by a research body external to the clinic**

Innovation carries an expectation of improved patient care, and duties to the medical profession, and society at large. Duties include contributions to knowledge, collaboration with peers and information sharing. \(^{130}\)

As the state of knowledge currently held about MSCs for musculoskeletal conditions is limited, offering this intervention beyond a clinical research trial would be considered to be innovative treatment. \(^{21} 106 115 116\) Innovative therapies are new or modified treatments undertaken in the best interests of the patient but with as yet unproven outcomes. Innovative practices are essential for medical progress, \(^{130}\) but should be subject to formal evaluation through rigorous peer-reviewed research. \(^{109}\) In the absence of robust research, innovative practices may become widely adopted without adequate data to determine risks and benefit; physicians are unable to determine safety and efficacy; and informed consent will be compromised. \(^{130}\)

The clinical use of MSCs as innovative therapy must be recorded, including indications for treatment, clinical and demographic data, and clinical outcomes. These should be open to

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Costs involved in MSC interventions used within research

The full cost of the procedure, including a full breakdown of costs will be provided to the patient. Costs involved in MSC interventions used within research will be declared.

Informed consent

In the interests of respecting patient autonomy, ACSP members are required to inform patients about all aspects of their care, including whether they are part of a research trial, or are receiving innovative therapy.

Any patients receiving MSC therapy under either pathway need to be made aware of and presented in writing the following:

- That MSCs are experimental and have not yet been proven to be safe or effective for clinical use.
- The long-term harms from the use of MSCs have not been determined.
- That the patient is being offered a therapy that has not been validated through reliable research methods.
- That identifiable personal patient or participant information and treatment will be entered into a database and accessed by researchers.
- That patients may be contacted at a later date for research purposes.
- That ethical approval will be sought prior to accessing patient data.
- Any conflicts of interest (including financial) held by the researcher or clinician providing innovative therapy will be declared.
- The full cost of the procedure, including a full breakdown of costs will be provided to the patient.
- Costs involved in MSC interventions used within research will not be passed onto participants as this has the potential to distort the research process.
- Informed consent to the procedure or to participation in research will be obtained in writing.

All advertising for services must meet the standards of the Australian Medical Council and the Medical Council of New Zealand.

This position statement will be reviewed and updated if necessary in 2017.

Summary

- Mesenchymal stem cell therapies are still under investigation.
- Research evidence to date suggests mesenchymal stem cells may be safe in the treatment of osteoarthritis and tendinopathies, so that it is reasonable to proceed to further robust clinical trials with rigorous long-term follow-up.
- There is limited evidence that suggests that non-expanded mesenchymal stem cell therapies do not work. Further research is required to determine the safety and efficacy of expanded mesenchymal stem cells with and without biological scaffolds/growth factors.
- There is currently insufficient evidence from high-quality clinical trials to recommend the clinical use of mesenchymal stem cell therapies for joint or tendon regeneration.

- The ACSP believes that robust knowledge generation is vital to improving patient care.
- The ACSP encourages the establishment of research studies to determine the safety and efficacy of mesenchymal stem cells for the treatment of musculoskeletal conditions.
  - Clinical research trials must be registered with an appropriate clinical research trial registry.
  - Any research trial must be subjected to peer review, and receive human research ethics committee approval.
  - Any and all research findings will be shared within the scientific and medical community including adverse outcomes.

- The ACSP position promotes patient safety and autonomy, endeavours to reduce potential harm to the patient, provides a level of clarity in an area of uncertainty, and takes responsibility for the advancement of knowledge.

- The ACSP position protects patients and the profession in the absence of unequivocal evidence regarding effectiveness and safety of these techniques, and yet responds to a recognised need to actively contribute to the development of knowledge in this area.

- The ACSP believes that any use of mesenchymal stem cells for musculoskeletal conditions must fit within either of the following pathways:
  - As part of a rigorous clinical research trial.
  - As an individualised innovative therapy. It is expected that only a few patients would go through this pathway before timely progression to clinical trials.

- The use of mesenchymal stem cells must only be undertaken within the expectations of the relevant medical regulatory organisations.

- ACSP members should engage in practices that permit open and transparent scientific evaluation of such services by an independent external research body.

- All indications for treatment, clinical and demographic data, and clinical outcomes should be open to scrutiny as part of a commitment to increasing knowledge and improving care.

- ACSP members must inform all patients receiving mesenchymal stem cell therapy that:
  - They are part of a research trial, or are receiving innovative therapy.
  - Mesenchymal stem cells are experimental and have not yet been proven to be safe or effective for clinical use.
  - The long-term harms from the use of mesenchymal stem cells have not been determined.
  - Identifiable personal patient or participant information and treatment will be entered into a database and accessed by researchers.
  - They may be contacted at a later date for research purposes.
  - Ethical approval will be sought prior to accessing patient data.
  - Any conflicts of interest held by the researcher or clinician providing innovative therapy will be declared.
  - The full cost of the procedure, including a full breakdown of costs will be provided to the patient. Costs involved in mesenchymal stem cell interventions used within research will not be passed onto participants.
  - Informed consent to the procedure will be obtained in writing.

Acknowledgements

The authors thank Alison K McLean BSc (Hons) LLB (Hons), Sydney Medical School, University of Sydney and Grant R Gillett, Professor of Biomedical Ethics, University of Otago for their invaluable contributions to this manuscript.
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Br J Sports Med  published online December 23, 2015

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