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Stem cell therapy for knee osteoarthritis: a narrative review of a rapidly evolving treatment with implications for physical therapy management

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ABSTRACT

Background: Stem cell therapy has emerged as a new, exciting treatment for repair of articular cartilage in osteoarthritis (OA), which currently has no cure. Regenerative cell therapies can potentially offer alternatives to total joint replacement for patients with OA. A variety of cell-based therapies have been developed involving the use of autologous and allogeneic mesenchymal stem cells (MSCs). To date, these stem cell therapies have been shown to be safe and efficacious, but information on the long-term clinical outcomes for joint function is lacking. Also lacking is information regarding post-treatment rehabilitation strategies and their effects.

Objectives: The purpose of this narrative review was to evaluate the current literature in relation to stem cell therapy for knee OA and to highlight the importance of physical therapists establishing and researching suitable care management and rehabilitation procedures for patients receiving stem cell therapy.

Major findings: The results of this literature review show that MSCs have been safe and effective at reducing pain and improving joint functionality and cartilage quality. The review also found that both autologous and allogeneic stem cells were able to produce similar clinical improvements in pain scores and cartilage repair and restoration. There is a lack of research evaluating the influence of rehabilitation on cartilage repair.

Conclusions: Current research shows that significant improvements in joint pain and function continue for approximately 2-year post-stem cell procedure. There is currently a lack of research into rehabilitation protocols which could potentially improve joint function further.

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Osteoarthritis; mesenchymal stem cells; joint pain; rehabilitation; exercise

Introduction

Osteoarthritis (OA) is the most common type of arthritis, affecting 10–15% of all adults over 60 years of age [1]. It is an inflammatory disease characterised by abnormal levels of pro-inflammatory cytokines such as interleukin-1 (IL-1) and tumour necrosis factor-α (TNF-α) [2]. Normal signalling levels of these cytokines promotes remodelling of tissues and tissue and organ homeostasis, but in chronic diseases, higher levels cause pain, faster tissue catabolism and exhaustion of resident stem cell niches [2]. OA is a whole-organ disease process affecting bone, articular cartilage and soft tissue elements of the joint [3]. Hallmarks of the disease process include joint space narrowing, osteophyte formation, development of bone oedema and progressive loss of articular cartilage. It is increasingly recognised that OA is a heterogeneous disease process with multiple distinct phenotypes [4].

OA is increasing in prevalence and is considered to be the fourth highest cause of disability worldwide [5]. There is currently no cure or effective disease modifying treatment and available treatments only act to relieve joint pain, not to repair the damaged tissue. Current treatments include analgesics, non-steroidal anti-inflammatory drugs (NSAIDs) or steroid injections directly into the joint [6]. Exercise and dietary management are also considered to be effective interventions [7]. Ultimately, many patients require joint replacement surgery due to increased problems with mobility or severe pain [8].

Autologous chondrocyte implantation (ACI) can be used to repair cartilage but it is a long process and the results are often inconsistent due to the low self-renewal and regeneration capacities of chondrocytes [9,10]. A recent proof-of-concept trial demonstrated the potential of mesenchymal stem cells (MSCs) to improve function, reduce pain and regenerate cartilage in participants with knee OA [11]. MSCs are immunoprivileged with immunosuppressive properties and may reduce inflammation by suppressing T-cell activity [12]. Therefore, stem cell therapy could help to decrease inflammation in OA, influencing the associated pain. A number of studies have been performed using different types of stem cells, demonstrating their potential value in

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repairing damaged cartilage and slowing the degenerative process [13]. The aim of this paper was to evaluate current research in this field and to provide a narrative review summarising the current state of knowledge and highlighting the need for physical therapists to develop and evaluate appropriate acute care management and rehabilitation strategies for patients undergoing stem cell therapy.

Stem cells

Stem cells are undifferentiated cells that are able to differentiate into many more specialised cell types and serve as an internal repair system to replenish other cells [13]. They are able to self-renew via cell division and can be induced to have particular functions. Stem cells were first discovered in human cord blood in 1978 [14] and since that time there have been many advances in stem cell research, evaluating their potential in treating a range of diseases [15]. A common use of stem cells is restoring the blood system after chemotherapy and other uses of stem cells being investigated are for treating spinal cord injury, other neurological conditions, cardiovascular disease and liver disease [13].

Embryonic stem cells (ESCs) are derived from the undifferentiated inner mass cells of blastocysts and are pluripotent, meaning they can differentiate into any cell in the body. Extensive research has been performed on mouse ESCs to study the stages of early development [16]. However, moral and ethical concerns surrounding human ESCs has limited research on this cell type and stimulated research into the potential of alternative adult stem cells, such as MSCs. MSCs are a form of adult stem cell that are multipotent, meaning they can differentiate into cells of a mesodermal lineage, for example, chondrocytes, adipocytes, osteocytes, myoblasts and tenocytes [12]. MSCs can be isolated from multiple locations, including bone marrow, adipose tissue, dental tissue and the umbilical cord and they are also found in synovial joints [17]. In 2001, they were isolated from synovial membranes and have also been isolated from meniscus tissue and articular cartilage in synovial joints [12,18]. MSCs play an important role in the maintenance and function of the joints and they can migrate to regions of inflammation and have anti-inflammatory and immunosuppressive effects as a result of their interaction with lymphocytes [12]. MSCs are being investigated as potential therapies for numerous conditions, including tendinopathy, OA, orthopaedic injuries and autoimmune disorders [13]. Wakitani et al. [19] showed that treating osteoarthritic joints with bone marrow MSCs resulted in the defective tissue being coated with soft white tissue resembling hyaline cartilage. MSCs can be introduced into the affected region in different ways, such as intra-articular injections and microfracture and implantation [12]. Centeno et al. [20] performed intra-articular injections of MSCs into OA knees and found decreased pain and increased cartilage volume in the joint in the months following the treatment.

Autologous stem cell transplantation involves collecting and freezing the patient's own stem cells pre-treatment and then transplanting these cells back into the body. This eliminates the need for immunosuppressive therapy as there is no risk of a graft versus host disease (GVHD) response, but the graft could be contaminated which could lead to relapse [21]. Allogeneic stem cell transplants involve the use of stem cells from a donor who is a close tissue match for the patient. Using allogeneic stem cells eliminates the morbidity associated with the procedures used for autologous cell collection (e.g. bone marrow sampling) and the cost associated [22]. However, there is a risk of GVHD and an immune response [21].

There are benefits to both autologous and allogeneic cell therapies and some studies have attempted to evaluate them comparatively. Studies have found that intra-articular injections of allogeneic MSCs have more significant side effects, or adverse responses, such as gait impairment and inflammation, than autologous MSCs [23,24]. However, allogeneic MSCs have also been found to be safe and effective at reducing pain and initiating cartilage regeneration [25]. Research related to the use of stem cells in the treatment of OA has been rapidly expanding since the mid-1990s and there is currently a major increase in research related to the clinical application of stem cell therapy [26]. It is becoming increasingly important for physical therapists to be familiar with this form of treatment and to develop clinical protocols and related research to optimise the rehabilitation and clinical outcomes for patients receiving this form of treatment. This approach has been termed regenerative rehabilitation [27].

Methods

A comprehensive review of existing literature relating to the effects of stem cells, specifically MSCs, on knee OA in humans. The primary searches were carried out using the databases PubMed, Web of Science and Science Direct. The literature searches were performed using keywords including 'knee osteoarthritis', 'stem cells', 'MSCs', 'autologous' and 'allogeneic'. Eligibility criteria included English-language papers which used stem cells as a method of treating knee OA. Exclusion criteria included papers

focusing on a joint other than the knee, animal studies, *ex vivo* studies and case studies.

Findings

All of the human studies that were reviewed, involving both autologous and allogeneic implants, indicate that stem cell therapy is relatively safe with only transient side effects, such as local discomfort, swelling and pain around the knee [8,25,28–30]. Adverse events were seen at a similar level to the control group [25] and so are thought to be attributed to the trauma of the injection rather than the stem cell treatments. A recent systematic review has concluded that intra-articular MSCs provide clinical improvements in pain and function at 1-year follow-up and that the majority of studies show improvements in cartilage function based on MRI and follow-up arthroscopy [31]. However, the authors emphasise that available evidence remains limited and more research is required [31]. Stem cells improved the quality of the cartilage in the knee joint in many studies, as evaluated by radiological examinations and MRI T2 mapping [29]. MRI T2 mapping is used to quantitatively measure the quality of the cartilage.

Stem cell treatments were also shown to significantly reduce the pain felt by individuals as demonstrated by clinical tests; visual analogue scale (VAS) pain rating [28], Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score [32], Knee Society Clinical Rating System (KSS) score [33] and Knee injury and Osteoarthritis Outcome Score (KOOS) [34].

One study detailed the results of a phase I–II trial using autologous MSCs to treat knee OA [28]. This study, along with others, confirmed the safety and feasibility of MSC treatment. The study tested 15 patients with grade II–III knee OA according to the Kellgren–Lawrence classification and treated them with autologous bone marrow-derived stem cells [28]. Bone marrow was harvested from patients' iliac crests under anaesthesia and the cells were culture expanded for 21 days to obtain around 40×10^6 viable MSCs. A single dose of $40.9 \times 10^6 \pm 0.4 \times 10^6$ cells in a final volume of 10 mL was then administered into the patients' knees via a medial parapatellar approach. Participants were then discharged from hospital and recommended to use crutches for 8 days.

As well as mild local discomfort around the knee injection site, some participants also experienced back and iliac crest pain due to the bone marrow extraction procedure [28]. However, this post-operative pain did not persist for longer than 72 h.

The VAS scores for pain during daily life and for pain on exertion were significantly improved 3 months after treatment. These values continued to decrease and maximum improvement was seen 6 and 12 months after the procedure. The baseline score for VAS for pain on daily activity was 58.27 mm and this was reduced to 19.47 mm after 12-month treatment and further decreased to 14.62 mm after 4 years. The WOMAC score, assessing pain, stiffness and function, also displayed significant improvements, decreasing from a score of 26 at baseline to 9 after 12 months [28].

Other studies using similar measures of pain and function have found similar results. Vega et al. [25] tested allogeneic bone marrow-derived MSCs in comparison with hyaluronic acid injection for OA treatment and used standardised mean difference (SMD) to compute a value for the improvement effect size. 0.2 correlated with a small improvement, 0.5 with a medium improvement and 0.8 with a large improvement. The SMD of the mean VAS scores in the MSC treated group was 0.77 and was 0.48 for the hyaluronic acid comparison group. Similarly, the SMD of the mean WOMAC-pain and WOMAC-total scores for the MSC treated group were 1.03 and 1.12, respectively, indicating a large, clinically important difference between the baseline score and the score 12 months after treatment. Values of all the test scores improved more with the stem cell treatment than with the control hyaluronic acid injection [25].

Spasovski et al. [29] tested the use of autologous adipose-derived MSCs for the treatment of knee OA and similar results were seen at 3 months after treatment. All of the participants reported a significant reduction in their VAS pain score for daily movement, which decreased from an average of 54.5 mm to 20.7 mm after 3 months. This decrease in pain was not only maintained, but further decreased to 9.1 mm, 18 months after treatment. Patients' average range of motion was improved by 17.3° in the first 3 months and a further 7.8° at the 6-month follow-up. The range of motion then decreased by 14.1° at the 18-month follow-up but was still higher than the baseline value. No other measures of functional improvement were taken. Participants were encouraged to carry out their normal daily activities during the study and to avoid physical therapy 1 month before, and 6 months after treatment but their degree of weight-bearing was not restricted.

A benefit of this study method using adipose-derived MSCs is that the cells were collected from subcutaneous fat from the superficial abdomen via a small and relatively non-invasive incision compared with the bone marrow extraction procedures.

Nevertheless, it still involved a two-stage operative procedure.

MRI evaluations of these MSC treatments have shown significant improvements in the quality of the cartilage tissue, cartilage repair and restructure [25,28,29]. Degradation of the cartilage matrix in OA causes a disruption of collagen which results in an increase in T2 relaxation time, which is quantitatively measured in milliseconds (ms) by T2 mapping. T2 relaxation values from 0 to 49 ms define normal cartilage, values from 50 to 99 ms are considered to be pathological. The mean relaxation values were sampled from 88 well-defined regions of interest (ROIs) around the knee [25,28]. The average relaxation time pre-treatment was 59.64 ms, indicative of pathological tissue and MSC treatments decreased this to 51.14 ms across the 12-month follow-up period. These results are suggestive of repair and regeneration of cartilage tissue. MRI results from other studies have exhibited significantly improved cartilage structure with fewer subchondral cysts and more uniform cartilage. No significant changes were observed on X-ray; however, there was no new osteophyte formation [29].

Another study [35] using patients with more severe OA, Kellgren–Lawrence grade III–IV, tested different doses of autologous MSCs for treatment. The groups receiving a high dose of cells were the only group to see statistically significant changes in the VAS and WOMAC scores. The VAS score was decreased from 79.6 mm at baseline, to 44.2, 33.3 and 45.8 mm at the 6-month, 1-year and 2-year follow-ups, respectively. The physical function subscale of the WOMAC questionnaire showed a similar pattern, decreasing from 38.8 at the baseline to 24.4, 11.2 and 13.4 at the same time points. There was no further improvement in these scores after 1 year, but this study showed that treatment with MSCs is able to improve knee function for up to 2 years as demonstrated by improvement in the function subscales of the WOMAC, KSS and KOOS. Similar to previous studies, regenerated articular cartilage, which was relatively smooth yet thin, was observed in the tibial and medial femoral condyles at 3 months and became smoother and thicker at 6 months. However, at 2 years, this regenerated cartilage was seen to be somewhat disrupted, particularly on the medial side. This highlights the importance of long-term follow-up studies to determine whether stem cell therapy significantly alters the long-term degenerative process. The volume of cartilage was significantly increased but it is not clear whether this was articular cartilage or fibrocartilage.

A benefit of autologous stem cell injections for patients is that there is no risk of immune rejection and therefore they do not require immune suppression after treatment. However, autologous stem cell treatments require two procedures, one to collect the cells, usually invasively from bone marrow, and another to introduce the cells into the knee joint. The cells also have to be expanded, which is time-consuming, so patients have to return for their second procedure after a period of time. This not only increases the trauma experienced but also the recovery time. In comparison, treatment with allogeneic stem cells requires just a single treatment with cells which can be prepared in advance, meaning that it is a shorter and less traumatic experience, which reduces the recovery time.

Rehabilitation post-stem cell therapy

Stem cell therapy is a relatively novel although very rapidly emerging approach to treating OA [26]. It is not widely accepted yet but with multiple large-scale clinical trials underway and with initial trials confirming safety and efficacy it may not be long before it is a more commonplace clinical procedure. With this in mind, it's important for physical therapists to consider post-treatment rehabilitation procedures in line with the concept of regenerative rehabilitation [27]. Other methods of cartilage repair such as ACI and microfracture/microdrilling have more extensive post-operative rehabilitation protocols, detailing instructions for how much weight bearing can be tolerated and for how long [36–38]. As stem cell therapy is in its infancy, there is still much that is not known, like the ideal dose of cells to be implanted [39], the long-term results and whether they would be impacted, either positively or negatively, by rehabilitation protocols. Randomised controlled trials (RCT) conducted to date have specifically avoided the inclusion of physical therapy treatment as a potential confounding variable in initial research [40]. However, a meta-analysis of non RCT studies showed that rehabilitation was a significant outcome modifier of MSC treatment, indicating the potential importance of an appropriate rehabilitation approach [40].

Post-operative care in patients undergoing the harvesting procedure for autologous stem cell treatment will be in line with standard procedures for bone marrow harvesting. Following stem cell implantation there is normally a period of non-weight bearing in order to allow for the implanted cells to become established and the tissue regeneration process to commence. Most trials to date have specifically avoided physical therapy treatment post-procedure in order to avoid confounding effects. It is clear that exercise is important for OA management and maintaining cartilage function, and also for maintaining adult stem cell numbers and

stimulating stem cell function in muscle and other tissues [41,42]. There is clearly a need for future research to evaluate the role of physical therapy management and exercise programs in the overall rehabilitation of patients undergoing stem cell treatment. In theory, appropriately controlled stressors applied to the knee joint during exercise might be an important stimulus for stem cell-mediated articular cartilage regeneration. Basic science research clearly demonstrates that immobilisation is detrimental to articular cartilage structure and function [43,44]. There is also a substantial body of research demonstrating that continuous passive motion (CPM), as originally proposed by Salter, can have a positive influence on cartilage repair and function [45]. A major systematic review of basic science studies related to CPM concluded that CPM improves the histological, histochemical, biochemical and biomechanical properties of repaired articular cartilage, leading to increased hyaline cartilage content in the repaired tissue [46]. This highlights the potential importance of movement in the rehabilitation of patients' post-MSC procedures.

Studies in rats evaluating the effect of treadmill exercise on the repair of cartilage defects with MSCs have shown that the parameters of post-operative exercise can have a significant influence on the quality of tissue repair [47]. Key elements of the exercise program that need to be carefully considered include the intensity of exercise, the degree of loading on the affected joint and the timing of exercise relative to the surgical procedure. Song and colleagues suggest that exercise should be of moderate intensity and that it should be commenced approximately 4 weeks after the surgical procedure [47]. Exercise loading at an earlier stage is likely to be detrimental and delaying the start of rehabilitation for 8 weeks or more minimises the potential benefit of exercise [47].

There is clearly scope for further basic science research in this field and for well-structured clinical studies to determine the most appropriate exercise prescription parameters. It is clear that factors such as joint loading, CPM, exercise intensity, timing of the exercise programs and exercise progression are likely to be of critical importance to ensuring optimal patient outcomes. It is also not clear whether the emphasis should be on resistance exercise or aerobic exercise or some combination since both local and systemic factors appear to be important in stimulating stem cell activity [42]. It is also not clear what role early passive motion might play in tissue regeneration and clinical outcomes. This is an area of research that is in its infancy but is likely to expand rapidly in coming years. It is important to understand whether movement and exercise is of additional value in relation to MSC therapy and to understand the intensity of exercise required and the duration of any rehabilitation program that is required to provide additional benefit.

Conclusion

Current research shows that significant improvements in joint pain and function continue for approximately 1- to 2-year post-stem cell procedures. There is a need for further large-scale RCTs to fully evaluate this relatively new therapeutic approach. Many trials are currently underway. There is also currently a lack of research into rehabilitation protocols which could potentially improve joint function further. Physical therapists should give consideration to developing appropriate protocols to manage these patients post-procedure and to evaluate the effects of additional exercise-based rehabilitation as a potential stimulus to further enhance the regenerative process following stem cell therapy. This is an area of critical importance in the new discipline of regenerative rehabilitation.

Disclosure statement

No potential conflict of interest was reported by the authors.

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