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A Review of the Literature on the Utilization of Stem Cells in Knee Osteoarthritis

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Abstract

Background: This literature review evaluates the utilization of various types of stem cells in the treatment of osteoarthritis.
Purpose: To assess the different types of stem cell therapy available in an attempt to determine its effectiveness and viability as a long term therapy option.
Methods: Articles were found by searching Augsburg Library Services, Google Scholar, and PubMed for recent, original studies using both allogeneic or autologous stem cells from a variety of cell lines including bone marrow and adipose tissue.
Conclusions: The utilization of stem cells as a viable treatment option for osteoarthritis shows improvement in pain management and return of function. Most studies showed an improvement in Visual Analogue Scale (VAS) and Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain scores, but did not show improvement to cartilage or bone features, evaluated by Kellgren-Lawrence scale. Despite this, stem cell use could provide a more effective alternative to therapy and pain management as well as a less costly, less invasive treatment than knee replacement surgery. The utilization of autologous stem cells helps with the accessibility of the treatment, however allogeneic options should still be pursued for those who may not be able to provide autologous cells. Further studies will need to be done to fully assess the long term effectiveness and viability of stem cells as a treatment option for osteoarthritis of the knee.

Key Words: Osteoarthritis, Stem Cells, Mesenchymal, Allogeneic, Autologous

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Introduction

Osteoarthritis (OA) is a debilitating disease that affects millions of people worldwide and leads to years of pain and lowered quality of life[1]. OA targets the joints most readily and among the joints, patients with knee OA constitute the largest share proportionally, with some 300 million worldwide[1]. While traditional treatment relies upon pain management through NSAIDs, acetaminophen, and corticosteroids, physical therapy combined with hyaluronic acid injection, and reconstructive surgery, the latest research suggests using stem cells to restore knee function and diminish symptoms associated with OA[2,3]. Stem cells may be derived from a number of sources, such as bone marrow, umbilical cords, or adipose tissue and may be further delineated between allogeneic or autologous cell lines[3,4,5].

As medicine continues to evolve and new best practices are developed the question of the long term effectiveness and viability in the utilization of stem cells for osteoarthritis in the knee must be addressed. To better understand this question this literature review will first look at a brief history of osteoarthritis, as well as look into studies utilizing stem cells as a treatment alternative comparing and contrasting their findings, and finally a look into what are ways in which the true value of utilizing stem cells for osteoarthritis can be accessed for their long term effectiveness and viability as an alternative practice.

This literature review outlines some of the research associated with stem cell use for treating knee OA, starting with trials with mice and progressing to the most current phase III human clinical trials from 2023. It considers the long term effectiveness and viability in the

utilization of stem cells for osteoarthritis in the knee. The research suggests that for the most part, stem cells, particularly mesenchymal stem cells (MSCs) derived from adipose tissue or bone marrow show promising results for alleviation of OA pain and symptoms but do not yet seem to have restorative function for chondrocytes or knee menisci evidenced by MRI and other imaging.

Methods

This comprehensive literature review was carried out utilizing Google Scholar, PubMed, Cinahl, Medline, and Augsburg Library Services. Search terms included “knee osteoarthritis”, “stem cell”, “autologous”, and “mesenchymal.” A single researcher screened and read the articles and no automation tools were used.

Included articles were published after 2018, were peer-reviewed, and reported primary research. For accessibility reasons, full articles also needed to be available, either from the search engine or through the Augsburg Library. Excluded articles included literature reviews, case studies, and meta-analyses. Studies that did not directly pertain to physiological outcomes for patients or animal models, such as an article about patient questions or readability of patient education materials, were also excluded.

Articles were broadly grouped into preclinical and Phase I/II/III clinical trials. They were also grouped by the types of stem cells utilized and differences in treatment methodology were considered. Study results accounted for sample size, significance, and subject outcomes.

Background/Literature Review

Osteoarthritis (OA) is a degenerative joint disease characterized by pain and loss of mobility[6]. It is caused by degradation of the cartilage on articular surfaces of the joint and has a high prevalence at 3.8%, affecting some 250 million people [6,7]. OA is exacerbated by age, obesity, a sedentary lifestyle, and genetic factors[6]. Knee osteoarthritis is the most common form, affecting 60% of OA patients, and is associated with greater morbidity and socioeconomic stress[7]. As such, research into alleviating knee OA could provide much scientific and medical utility.

Current treatments for knee OA focus on alleviating symptoms through pain management and physical therapy[8]. As the condition progresses, treatment options turn to glucocorticoid injections and ultimately, knee replacement[8]. These treatments come with significant drawbacks. None of these treatments are regenerative and only delay degradation of the knee towards replacement[9]. Knee replacements may function for a time, but may need to be replaced and are unattractive to younger patients[5]. Even when performed, knee replacement is associated with increased risk of surgery and does not completely restore mobility[5].

Researchers studying knee OA often utilize a variety of scales and metrics to quantify baseline values and results. These scales measure pain, OA outcomes, and degree of physical degradation. The first and simplest of these is the Visual Analogue Scale (VAS). VAS, first introduced in 1921, allows a quick assessment of pain[10]. Patients are asked to mark on a line from 0 to 10 how much pain they are in[10]. Next, the Kellgren-Lawrence assesses radiographs of OA based upon the presence of osteophyte, narrow joint space, bone cysts, and bone end sclerosis[11]. The most widely used scale for OA, it allows a physician to rate the degree of degradation from OA from 0-4 with Grade 4 being the most severe[11]. Meanwhile, the Western Ontario and McMaster Universities Arthritis Index (WOMAC) evaluates the degree of OA based

on a questionnaire[12]. It asks patients to rate the difficulty of different activities such as walking, putting on socks, or getting out of bed, from 0-4 with 4 being extremely difficult[12]. With 24 questions, the scores range from 0-96. Finally, the Knee Injury and Osteoarthritis Outcome Score refines the WOMAC into a 42-question questionnaire, split amongst five categories: Pain, Symptom, Activities of Daily Living, Sport, and Quality of Life[13]. Many of the studies cited would use some combination of these metrics, although others were less commonly used as well.

In order to treat knee OA, this review emphasizes the use of stem cells, specifically mesenchymal stem cells (MSC). Stem cells may function well as therapeutics for their ability to differentiate into any cell type[1]. Of the stem cells, MSC are attractive despite their lower pluripotency due to their ability to remain undifferentiated until injection, whereupon they modulate into chondrocytes[1]. While the exact mechanism of action is unknown, MSC may support cartilage regeneration by differentiation into chondral tissue[14]. They may also have immunomodulatory effects, helping suppress inflammation by inhibiting some leukocyte function[15]. Further, some research suggests that MSC injections help diminish the effect of lower MSC counts in the untreated knee[4].

In most of these studies, stem cells were derived from a variety of tissue types. None are without advantages or disadvantages. Thus far, bone marrow-derived MSCs are the most commonly used for treating knee OA[9]. Rich in both mesenchymal and hematopoietic stem cells, bone-marrow offers many growth factors, cytokines, and related cells to help restore the extracellular matrix and improve patient outcomes[1]. However, bone marrow extraction is inefficient, with less than 0.01% of cells extracted being MSC and requires an invasive procedure [6,9,].

As an alternative, umbilical cord-derived MSCs may be a promising option, with easy extraction, fast differentiation and growth, and abundant growth factors such as epithelial growth factor and collagen[6]. The cords themselves can be stored and preserved more readily[9]. Less research has been performed upon umbilical cord-derived MSC, however, and they sometimes produce a lower output than other MSC types[6]. Still, given their tissue repair properties, umbilical cord-derived MSCs may yet prove to be an important source of stem cells. It should be noted, however, that while extraction is painless, consent and ethical issues may arise. Despite the potential positive attributes of umbilical cord-derived stem cells (UC-MSC), they exhibit earlier morphological changes and a faster loss of amplification ability compared to other sources of stem cells, they also have lower attachment efficiency, which impacts their proliferation and differentiation capabilities. This lower attachment efficiency also makes the process of isolating and expanding them to therapeutic levels more challenging. The lower overall output of functional UC-MSCs compared to MSCs derived from other sources indicates that either more research would be required to try and rectify these shortcomings, or the future of stem cell usage for osteoarthritis in the knee lies elsewhere[6].

Adipose-derived MSC, meanwhile, offer some choice advantages. They are more readily collected with high yields and can often be autologous[16]. Their preparation can be more efficient, at times even performed bedside[2]. While subcutaneous adipose tissue seems to be more common, some research suggests that cells derived from the infrapatellar fat pad present greater regenerative properties[1]. However, despite their efficiency, they have a lower potential for differentiation[1]. While the article does not specifically address why cells extracted from the infrapatellar fat pad have a lower potential for differentiation, it does state that MSC derived from different locations and sources have intrinsic differences in gene expression and surface

marker profiles. These differences can affect the cells capacity for proliferation and differentiation which could account for this finding[1].

In addition, a number of proprietary cell products have been used to treat knee OA. Studies examining allogeneic ELIXCYTE®, a novel adipose-derived stromal vascular fraction, and ReJoin®, an adipose-derived MSC suspended in a novel suspension, show positive effects on patient outcomes[3,2,17]. These studies accounted for number of doses, cells per dose, degree of OA degradation, and patient-reported pain. Meanwhile, other studies focused on bone marrow as a source for stem cells. In 2018, Lamo-Espinosa et al. considered the use of hyaluronic acid with bone marrow-derived MSC[18]. Hyaluronic acid was used due to its contribution to synovial fluid[1]. They saw marked improvement in VAS and WOMAC score[18]. Their findings were supported by Chahal et al[19]. They also used autologous bone marrow-derived MSC to treat knee OA and reported improved pain scores[19]. Greater examination of patient laboratory test values provided evidence for reduced inflammatory and fibrotic markers[19].

However, later studies would emphasize some of the difficulty with which bone marrow would be obtained as well as some of the inflammatory risks they pose if not properly prepared[1]. Also, none of these studies showed significant improvements to cartilage regeneration via Kellgren-Lawrence score[19,1]. In addition, some MSC studies could not produce significant differences between MSC treatment and a placebo. In 2020, Lamo-Espinosa repeated their trial with platelet rich plasma as solution[4]. This study found significant improvements in VAS and WOMAC scores in both the MSC and placebo groups but no significant difference between the groups, suggesting that injections of platelet rich plasma alone could help alleviate pain symptoms[4]. This conclusion is supported with prior literature and current clinical treatments[6].

More recent studies from 2019 emphasized the adipose-derived cell lines. Lee et al. found that these MSC improved WOMAC and VAS scores at 6 months but with no improvement to Kellgren-Lawrence MRI scores[20]. Their target dosage was greater than some of the bone marrow-derived MSC studies at $1x10^8$ cells[20,19]. Larger studies (N=261) confirmed these findings over 6 months[21]. Another 2019 Phase I/II trial found adipose stem cells improved WOMAC and KOOS scores at 12 months[15]. Interestingly, they found that a single injection produced more consistent improvements than multiple injections over the year, suggesting that MSC dose does not linearly scale with improvement[15]. These findings are contrasted with other studies that report pain score and cartilage differences in MSC dose were significant after 48 and 96 weeks[14,22]. In one case, an injection of $5x10^7$ cells showed a significantly greater improvement to pain scores than $1x10^7$ or $2x10^7$ cells[22].

Other cell lines were also considered. Umbilical-derived MSCs were shown to improve pain scores but not Kellgren-Lawrence after 6 months[9]. Stromal vascular fraction, where adipose-derived MSCs are fractionated to a concentrated MSC dose, had significant improvements against a placebo[2]. Again, however, no change in cartilage thickness via MRI was observed[2]. The proprietary allogeneic ELIXCYTE® and ReJoin® both showed improved WOMAC and VAS scores[3,17]. Notably, the ReJoin® study offered one of the few results that showed increased cartilage thickness about the knee[17]. As presented by the study, an increase in cartilage volume does not by itself denote an improved health outcome, but combined with the improved WOMAC and VAS pain scores, it could offer a promising line of study[17]. However, despite the proprietary studies reporting promising results, other studies showed that allogeneic lines were not as viable as autologous lines[6]. They also question whether the more common bone marrow treatments would be better served through adipose-derived MSC.

To resolve some of these questions, one of the more recent studies compared the use of autologous bone marrow-derived and adipose-derived MSC[23]. While this study found significant improvement to KOOS and VAS score regardless of cell line, no significant difference between the treatments was found[23].

Discussion/Analysis

Mesenchymal stem cells offer many advantages to other treatment types. In each study, significant improvement to VAS, KOOS, and WOMAC scores were significant, signifying greater patient outcomes and reported pain. Prior research suggests that this is due, in part, to the regenerative potential of MSC and the anti-inflammatory effects that their source tissues provide[2]. Likewise, MSC harvesting and injection is a minimally invasive procedure, especially when contrasted with knee replacement surgery[6]. While the previous studies did not come to a consensus about preferred cell lines, autologous or allogeneic, or injection solution, the variety of possible treatment types could offer a greater potential for personalized treatments, whether for unique patient needs or to adjust to specific costs[5]. When considering cost, especially, a first of its kind study found that MSC treatments, specifically umbilical-derived MSC, provided a cost effective treatment for knee OA under a quality-of-life and societal benefit lens[5]. They found that MSC treatment would prove cost effective for both the individual and society at large when considering direct costs of the operation, time, productivity loss, utility values for the state, and survival functions[5].

Table 1. Summary of the advantages and disadvantages of different MSC sources[6].

	Advantages	Disadvantages
Bone Marrow	● Widely used, large body of research ● High differentiation ● Possess growth factors ● May be autologous or allogeneic	● Low yield ● Invasive collection
Adipose Tissue	● Easily harvested in large quantities ● Autologous or allogeneic	● Low differentiation ● Lower expression of certain growth factors ● Compatibility concerns with high HLA expression
Umbilical Cord	● Rapid proliferation ● Pain-free extraction ● Highly differentiable ● Ample growth factors	● Inherently allogeneic ● Ethical and supply concerns

However, MSC treatment comes with some notable disadvantages. Some studies showed that the efficacy of MSC injections degraded after 6 months, refuting a significant regenerative potential[9]. Few of the studies produced significant improvements to cartilage thickness. Despite that, no studies showed a correlation between WOMAC and VAC score improvements and an increase in cartilage volume. Further studies examining the relationship between outcomes and cartilage thickness, if any, should be continued.

Of the articles cited, the only studies that showed a change used more advanced, higher resolution MRI techniques, suggesting that any change was too small to be detectable by more traditional means[17,14]. Likewise, the heterogeneity and variability of MSC can prove to be a disadvantage, as allogeneic MSC can make poor antigen or HLA matches to the recipient, degrading patient outcomes[3]. Also, for how temporary the improvements to pain and function MSC treatment provides, at approximately $15,000 it may be more cost effective to perform more invasive procedures[5]. One review considers MSC with an artificial scaffold to treat knee OA[24]. Since much of the articular cartilage in the knee is composed of an extracellular matrix, a

scaffold can help provide a frame upon which new cells may be regenerated[14,24]. This procedure, while more invasive than MSC injection, has begun producing promising results[24]. Other treatments vary the scaffold, sometimes proprietary or formed from an osteochondral graft, but so far, these studies are in the very early stages of clinical trials[24].

Research into MSC treatment for knee OA is so far at an early stage and will require additional refinement. With respect to cost, no studies were found addressing the cost effectiveness of stem cell treatment against other, high-cost, more invasive procedures. Research will need to be done on how MSC treatment compares to other treatment options for pain, function, and imaging. The early results from Phase III studies that are just starting to appear need to be carried forward to address safety and viability concerns, especially to see if additional injections may be needed over time. However, these early results show the potential of stem cell research and with modification, may still provide both cost-effective and viable treatment.

Conclusions

This literature review looked at the utilization of stem cells as a treatment for osteoarthritis, in an attempt to determine its long term effectiveness and viability. While most studies seem to indicate that the utilization of stem cells in treatment is effective as a therapeutic option seeing a significant impact in pain control and an increase in functionality of the knee, others contradict these findings, stating that little difference has been seen in comparison to other treatments. Few of the studies showed any improvement to cartilage thickness or MRI quality on the Kellgren-Lawrence scale. The long-term effectiveness of MSC treatment is in doubt, and different treatment protocols may need to be considered. The cost is exorbitant, comparable initially to knee replacement surgery[5]. However, when accounting for improved quality of life,

improved productivity, reduced work absenteeism, and reduced ongoing costs, MSC treatment has been modeled to have greater patient and societal cost effectiveness[5].

Despite this, the research reviewed here does tend to suggests that, stem cells, particularly mesenchymal stem cells (MSCs) derived from adipose tissue or bone marrow do show promising results in the alleviation of pain caused by OA, but do not yet seem to have restorative function for chondrocytes or knee menisci evidenced by MRI and other imaging. Continuing these studies and the monitoring of the patients post treatment will help to determine the true long term effects of stem cell utilization.

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