ART & TECHNOLOGY PUBLISHING PTE. LTD.

Cell Biology Research
2022 Volume 3, Issue 1
ISSN: 2529-7627(Online)
ISSN: 2529-7643(Print)

Mechanical Stress Research and Regenerative Rehabilitation after Mesenchymal Stem Cell Treatment in People with Knee Osteoarthritis

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Abstract

Mesenchymal stem cells (MSCs) have emerged as a cell type with great potential for cell-based articular cartilage repair in patients with knee osteoarthritis (OA). However, a meta-analysis of clinical trials of the MSC treatment revealed that current evidence about articular cartilage regeneration and objectively measured functional improvement in people with knee OA was inconclusive. Research for regenerative rehabilitation, a recently emerged interdisciplinary field, could contribute to establishing effective cell-based therapy that maximizes cartilage regeneration and functional improvement in people with knee OA. We herein summarize our cross-disciplinary approaches toward establishing effective regenerative rehabilitation in MSC-based treatment for people with knee OA. This review would serve as the foundation for future studies investigating the effects of rehabilitative approaches in regenerative medicine that lead to the clinical success of cell-based treatment.

Keywords

Knee osteoarthritis
Articular cartilage
Mesenchymal stem cell
Regenerative rehabilitation
Exercise

1. Introduction

Knee osteoarthritis (OA) is a musculoskeletal disorder primarily characterized by degeneration and wear of articular cartilage, causing joint pain and functional impairment [1,2]. In the 2014 guidelines from the Osteoarthritis Research Society International (OARSI), exercise-based rehabilitation, in conjunction with weight reduction, patient education, and muscle strengthening

training, is recommended as the first choice for non-pharmacological treatment for knee OA patients [3]. Such exercises are commonly performed as symptom-relief therapy to alleviate joint pain in knee OA patients. A Cochrane systematic review from 2015 concluded that exercise over a 2 to 6-month period for knee OA patients has a low to moderate pain reduction effect, similar to non-steroidal anti-inflammatory drugs (NSAIDs) [4,5].

Exercise that involves mechanical stress has a chondroprotective effect and has been shown in experimental studies using knee OA animal models to prevent the worsening of joint cartilage degeneration [6-8]. In the context of such findings, randomized controlled trials involving human subjects have emerged, assessing exercise as a disease-modifying treatment, with a focus on evaluating joint cartilage morphology and constituent components (proteoglycan, type II collagen), inflammation, and molecular markers related to joint cartilage matrix [9,10]. Furthermore, the emergence of the interdisciplinary field of regenerative rehabilitation has brought forth the recognition that exercise-centered rehabilitation plays a crucial role in guiding cartilage regeneration through stem cell therapy [11,12].

This study first introduces research on mechanical stress in knee OA cartilage and explains the strength-dependent protective and destructive effects on joint cartilage by exercise and its molecular mechanisms. Subsequently, the potential of rehabilitation (regenerative rehabilitation) in knee OA cartilage regeneration therapy using mesenchymal stem cells (MSCs). Finally, the exercise function assessment developed in collaboration with medical engineering is introduced, as well as the author's personal views on the direction that research in regenerative rehabilitation for knee OA aims to achieve.

2. Biological response of knee OA cartilage to exercise and exploration of molecular mechanisms

2.1. Exercise protects or damages knee OA cartilage depending on intensity

Knee OA has long been considered a "wear-and-tear disease," with the severity of joint cartilage degeneration thought to be directly proportional to the amount of mechanical stress applied to the joint. If this concept was correct and articular cartilage was merely a shock absorber, it would not be surprising for the extent of cartilage degeneration to increase in proportion to the intensity and duration of exercise. However, a placebo-controlled randomized trial reported in 2005 revealed that a 4-week exercise therapy for 30 patients who had undergone medial meniscus resection 3–5 years earlier increased the amount of glycosaminoglycans (dGEMRIC value) in the articular cartilage, as seen on magnetic resonance imaging (MRI) [13]. In other words, even in high-risk groups with knee OA after medial meniscus resection, an exercise that applies mechanical stress does not necessarily promote joint destruction and may potentially demonstrate a protective effect on the joint cartilage, depending on the exercise conditions. The idea that exercise is not necessarily harmful to knee OA cartilage is supported by a meta-analysis reported in 2018 [9,10]. Such findings challenge the notion that known OA is simply a "wear-and-tear disease".

In avascular tissues such as joint cartilage, cellular metabolism relies significantly on the synovial fluid present in the joint cavity. Through the repetitive loading and unloading of weight on the cartilage, which occurs during exercise, synovial fluid flows in and out of the cartilage. As a result, various types of mechanical stress, such as compressive stress, tensile stress, and shear stress, affect the chondrocytes [14]. Different mechanical stresses applied to chondrocytes induce biological responses through mechanoreceptors present on the cell membrane [15]. For example, intermittent compression stress (at 10% strain) applied to cartilage-like three-dimensional (3D) tissues suppresses the gene expression of a disintegrin and metalloproteinase with thrombospondin motifs 5 (ADAMTS5), an enzyme responsible for cartilage degradation. However, inhibiting the function of the mechanoreceptor transient receptor potential vanilloid 4 (TRPV4) on

the cell membrane cancels the gene expression of ADAMTS5 caused by compression stress [16]. In other words, the cartilage-protective effect of compression stress is produced through cellular mechanoreceptors. Thus, the aforementioned protective effect of exercise on articular cartilage can be easily explained from a molecular biological perspective. It is important to understand the biological response of articular cartilage to mechanical stress.

It is imperative to determine the biological responses of knee OA cartilage to mechanical stress of various intensities. However, capturing subtle changes in articular cartilage in clinical studies involving humans is challenging. Hence, an animal model of traumatic knee OA was established in 2014, where medial meniscus instability was surgically induced [17]. In this model, the loss of shock-absorbing function by the medial meniscus results in increased stress on the medial tibial femoral joint surface [18], inducing traumatic knee OA. These model animals were subjected to treadmill exercise under various running conditions for 4 weeks (30 minutes per day, 5 days per week) and histologically evaluated the continuous changes in articular cartilage. As a result, moderate-intensity treadmill exercise (12 m/min) prevented the loss of proteoglycans, a major component of the articular cartilage matrix, and delayed the progression of knee OA. However, high-intensity treadmill exercise (21 m/min) promoted the loss of proteoglycans and accelerated the progression of knee OA [7].

In previous experimental systems involving treadmill exercise loads on knee OA animal models, the relationship between exercise intensity and histological signs of articular cartilage degeneration has been found to be nonlinear and U-shaped [6,7]. Similarly, collagen type II cleavage product (C2C) and procollagen IIC propeptide (CPII), which are the breakdown and synthesis markers of type II collagen, a major component of articular cartilage, were measured by enzyme-linked immune sorbent assay) and the ratio C2C/CPII was evaluated in relation to exercise intensity, a similar nonlinear and U-shaped relationship was observed [19]. In other words, excessive exercise can exacerbate already established knee OA, while moderate exercise has the potential to prevent its progression. Based on the results of these animal studies, it can be considered that exercise, at least at the protein level, has an intensity-dependent manner to protect from damaged knee OA cartilage.

2.2. Exploration of the molecular mechanisms of cartilage protection and damage by exercise

The mechanisms behind the intensity-dependent effects of exercise have not been fully elucidated. However, in experimental systems where compressive stress was applied to extracted articular cartilage plus or 3D cartilage tissue, several candidate factors have been identified [20-23]. For instance, in a study by Madej *et al*., when physiological (3 MPa) and excessive (12 MPa) compressive stress was applied to an articular cartilage plug model cultured in synovial fluid from knee OA patients, only the former resulted in increased gene expression of bAlk5, a type I receptor for transforming growth factor-beta (TGF-β) [21]. Furthermore, in a study by Nam *et al*., using a model where interleukin 1-beta (IL-1β), an inflammatory cytokine, was introduced to 3D cartilage tissue embedded with C3H10T1/2 cells, which are fibroblast-like cells derived from mouse embryos, the application of physiological (10% strain) and excessive (30% strain) compressive stress had differing effects. The former suppressed the phosphorylation of IκB-α, inhibiting the activation of inflammatory signaling pathways through the nuclear translocation of NF-κB, while the latter exacerbated this process [22].

The experimental systems using the aforementioned articular cartilage plug model and 3D cartilage tissue have been significant in elucidating the biological responses of chondrocytes to pure mechanical stress. However, within the knee joint in the living body, articular cartilage interacts biologically with other joint tissues, especially with the subchondral bone [24].

Consequently, these models alone may not be sufficient, and it is essential to conduct molecular mechanisms using knee OA animal models. Therefore, the molecular mechanisms behind the chondroprotective of moderate-intensity treadmill exercise were explored using the medial meniscus instability animal model. It was observed that moderate-intensity treadmill exercise increases bone morphogenetic proteins (BMPs) in the superficial layer of articular cartilage [25]. Based on this observation, it was hypothesized that the increased expression of BMPs plays a role in the chondroprotective effect. To test this hypothesis, intra-articular administration of Gremlin-1, a BMP antagonist, before the moderate-intensity treadmill exercise was conducted. This led to a reduction in the chondroprotective effect induced by the exercise [7]. This result supports the earlier hypothesis and suggests that growth factors such as BMPs may play an important role in the chondroprotective effect of exercise. It is essential to note that in this animal study, the effect of exercise load may not be solely attributed to mechanical stress. Nevertheless, it is worth noting that even in experimental systems where mechanical stress was applied solely to cartilage, there have been reports of enhanced BMP gene expression in chondrocytes [26].

From a molecular biology perspective, exercise does not necessarily exacerbate knee OA cartilage degeneration. Reports are indicating that the progression of traumatic knee OA induced by meniscal instability can be suppressed by either disabling the release of cartilage-degrading enzymes from chondrocytes or by inducing the apoptosis of chondrocytes in the superficial layer of cartilage [27-29]. In other words, in the onset and progression of knee OA, the cartilage-degrading enzymes released by chondrocytes themselves play an important role. This raises questions about how to control chondrocyte metabolism and how exercises should be reconsidered. A reevaluation of exercise from a molecular biology perspective is essential not only in the context of knee OA but also in the field of regenerative rehabilitation, to maximize the therapeutic effects of stem cell-based treatments.

3. Rehabilitation possibilities in regenerative medicine for knee OA

3.1. Regenerative rehabilitation

The concept of "regenerative rehabilitation" emerged as a new interdisciplinary field, introduced to the world by Fabrisia Ambrosio of the University of Pittsburgh in the United States [11]. Regenerative rehabilitation is an emerging interdisciplinary field that combines regenerative medicinal techniques with rehabilitation medicine to innovate and enhance tissue recovery and functional improvement. Stephen Badylak of the University of Pittsburgh has emphasized that rehabilitation is essential to realize the proper effect of transplantation therapies [30]. Although details are given in other references [31,32], animal studies have demonstrated that the rehabilitation approach promotes the tissue regeneration effects of stem cell therapy in animal models, including skeletal muscle defects [33], muscular dystrophy [34], traumatic brain injury [35], stroke [36], and spinal cord injury [37]. It was also confirmed in an animal model with articular cartilage defects that rehabilitation approaches can promote the cartilage regeneration effects of MSC therapy [38,39]. In November 2018, Fabrisia Ambrosio from the University of Pittsburgh and Thomas A. Rando from Stanford University served as guest editors for a special issue in the Nature partner journal Regenerative Medicine [40], a specialized academic journal in regenerative medicine. This special issue covered the concept of regenerative rehabilitation and included a meta-analysis paper [41]. By sharing the concept of regenerative rehabilitation with academics involved in regenerative medical research, it is anticipated that the development and practical application of regenerative medicine research will be accelerated.

3.2. Regenerative rehabilitation following mesenchymal stem cell transplantation in knee OA patients

MSCs are present in various tissues within the body and possess the ability to differentiate into cells of

mesenchymal tissues such as bone, cartilage, and adipose tissue. Research into knee OA cartilage regeneration using MSCs has been on the rise in recent years. As of the end of March 2019, the number of clinical trial registrations for MSC therapy targeting knee OA in the U.S. clinical trial database, ClinicalTrials.gov, has exceeded 60.

To understand the extent of MSC therapy regenerate knee OA cartilage in these clinical trials, and if there were any additional effects when combined with rehabilitation, a meta-analysis of 35 clinical trials reported until August 2017 that examined the effectiveness of MSC therapy for knee OA patients was collected and conducted [41]. The results of this meta-analysis revealed three key findings:

(1) Quantitative improvement in knee OA cartilage (increase in articular cartilage volume) due to MSC therapy is limited and characterized by a low standardized effect size.
(2) Trials that combined MSC therapy with rehabilitation showed approximately a 70% higher improvement in subjective physical function compared to cell therapy alone.
(3) Objective and quantitative assessments of post-MSC therapy physical function were lacking [41].

It is important to note that detailed descriptions of rehabilitation were lacking in some cases. However, in clinical trials involving human subjects, the potential for rehabilitation to enhance the subjective improvement in physical function resulting from cell therapy is a noteworthy finding.

As revealed in the meta-analysis [41], strategies to enhance the cartilage regeneration effect in MSC therapy for knee OA are now being sought. So far, it has been shown that mechanical stress can enhance paracrine effects and cartilage differentiation abilities of MSCs [42,43]. Additionally, knee joint traction using external fixation has been found to enhance the articular cartilage regeneration effect of MSCs [44,45]. In other words, by optimizing the mechanical stress environment within the joint and establishing the microenvironment around the cells through rehabilitation, it may be possible to make progress toward addressing the challenges mentioned earlier.

Currently, in Japan, the conditions covered by insurance for autologous cultured chondrocyte transplantation are for traumatic articular cartilage defects or osteochondritis dissecans, and knee OA is not included. Nonetheless, intending to expand its application to knee OA in the future, the author aims to lead the way in advancing regenerative rehabilitation research for knee OA ahead of the world.

4. Challenging the establishment of new functional assessments for regenerative rehabilitation in knee OA

As mentioned in the previous meta-analysis [41], there is a lack of objective and quantitative assessments of functional capabilities in the context of MSC therapy for knee OA. Furthermore, at the 7th Annual International Symposium on Regenerative Rehabilitation held in Seattle in November 2018, there were no research presentations concerning such functional assessments. Since the concept of regenerative rehabilitation revolves around maximizing functional recovery through tissue regeneration [31], it was believed that achieving the academic development and clinical integration of regenerative rehabilitation cannot be accomplished without quantitative evaluation of these functional improvements.

While there is no definite answer to the types of functional assessments that are important in the context of regenerative rehabilitation at present, a valuable reference can be found in the recommendations for functional assessment scales published by the OARSI in 2013 [46]. These recommendations suggest comprehensive assessments that address various tasks, including rising from a chair, walking short distances, climbing stairs, and walking longer distances [46]. Additionally, knee OA patients are known to exhibit changes in spatiotemporal gait parameters such as extended stride time and reduced cadence [47], along

with kinematic alterations in proximal joint segments, particularly in trunk lateral lean [48].

As such, attempts to develop and implement measurement algorithms that allow the assessment of spatiotemporal gait parameters and gait in various tasks using small and easily deployable sensors for practical clinical use have been carried out. For instance, the Laser-TUG (Timed Up and Go) system was developed using a laser ranging sensor [49]. The Laser-TUG system involves placing a small laser range sensor under the chair used for TUG testing. This sensor emits infrared light that is reflected by the subject's legs during the TUG test, allowing information on the position and velocity of the subject's legs to be obtained in a two-dimensional manner. This enables the calculation of spatiotemporal gait parameters for each TUG subtask (rising from the chair, walking, turning, sitting) [49]. Originally developed to assess the mobility of elderly individuals living in the community [50], this measurement system was adapted to evaluate the mobility characteristics of knee OA patients. Through multivariate analysis, the mobility characteristics of knee OA patients were assessed during each TUG subtask. The results revealed that knee OA patients with weakened hip abductor muscle strength had slower TUG turning speeds [51]. This demonstrates that Laser-TUG can capture mobility characteristics in knee OA patients that cannot be assessed by TUG completion time evaluation alone. Moreover, while not directly related to TUG, by attaching inertial sensors to the lower trunk, an index of left-right asymmetry calculated from the lateral acceleration component generated in the lower trunk during straight-line walking is associated with daily life impairment in knee OA patients [52]. These assessment indices have proven valuable for evaluating the effectiveness of outpatient physical therapy for knee OA patients through collaboration with medical institutions.

The assessment systems mentioned earlier are designed for level walking and turning tasks. However, attempts to develop and implement measurement algorithms for the challenging task of stair ascent and descent have been ongoing. Stair climbing is considered to require high knee joint torque and is known for its high task difficulty [53,54]. While the stopwatch-based stair climb test is a widely accepted and reliable method for assessing stair climbing performance [55], it has been suggested that measuring completion time alone may lack sensitivity to therapeutic effects [56]. Knee OA patients often employ strategies to reduce knee joint torque during stair ascent and descent [57]. Therefore, a stair climb assessment system that combines kinematic and kinetic evaluations with completion time measurements may prove valuable for evaluating knee OA patients. To this end, depth sensors that emit infrared light were utilized to capture trajectory information of each join and whole-body skeletal information during stair ascent and descent [58]. Kinematic features were in the process of extraction, and the usefulness of this data was validated for assessing knee OA patients and determining treatment effects.

These exercise function evaluation systems are still under development, and there are many challenges to overcome for practical implementation. Nevertheless, all the exercise function evaluation systems introduced in this paper use inexpensive, small sensors, offering the significant advantage of a low barrier to entry for real clinical use. With a clever collaboration between medicine and engineering, the efforts in constructing useful exercise function evaluation methods were aimed at assessing the effectiveness of regenerative rehabilitation in knee OA.

5. Conclusion

In the success of next-generation knee OA cartilage treatment using MSCs, the development of regenerative rehabilitation is essential. Exercise, which plays a central role in physical therapy, has the potential to control the metabolic activity of chondrocytes and mesenchymal stem cells. Therefore, research aimed at understanding the molecular mechanisms and

establishing effective exercise prescriptions is needed.

This paper has explained the new possibilities that exercise holds from a molecular biological perspective. However, there are very few physical therapists engaged in research from such a perspective. To encourage physical therapists' participation in the field of regenerative rehabilitation, it is necessary to enhance systematic educational curricula for research in undergraduate education. In the United States, the Alliance for Regenerative Rehabilitation Research and Training (AR^3T), organized in 2016, systematically provides education and research grants related to regenerative rehabilitation. Under the principle of out-of-the-box thinking, continuous challenges and knowledge transfer to younger generations are believed to contribute to academic development in this field and promote the involvement of Japanese physical therapists in research.

Disclosure statement

The author declares no conflict of interest.

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