The Effects of Space Microgravity on Hip and Knee Cartilage: A New Frontier in Orthopaedics

ABSTRACT

Introduction: Given the expansion of commercial and recreational space exploration, orthopaedic surgeons will need to understand the implications of microgravity on cartilaginous damage and to anticipate the resulting pathology from accelerated chondrolysis.

The purpose of this systematic review is to evaluate the effects of space and microgravity on hip and knee articular cartilage, including its impact on joint mobility and functional status.

Materials and Methods: A review of the current literature was performed utilizing the terms “joints,” “joint mobility,” “articular cartilage,” “knee,” “hip,” “space,” “microgravity,” and “osteoarthritis” in PubMed and
Given the recent interest in expansion of commercial and recreational space travel, physicians and scientists have become increasingly interested in the effects of reduced gravity and solar radiation on the human body, including articular cartilage of major weight-bearing joints. As a result, novel bench, translational, and human research studies have been conducted to evaluate the relationship between microgravity and physiologic processes, including initiatives by the National Aeronautics and Space Administration (NASA). Microgravity environments can result in a variety of adverse physiologic effects, including cardiovascular dysfunction, impaired immune responses, visual impairments, and genitourinary complications. However, few previous studies have investigated the specific cartilaginous changes that occur and the impact that these have on major joints, particularly the hip and knee.

As defined by Fox et al., cartilage is a durable, smooth connective tissue comprised of a dense matrix of collagen and elastic fibers within a ground substance, collectively known as the extracellular matrix (ECM). At the cellular level, mesenchymal progenitor cells, known as chondroblasts, are responsible for secreting the components of this ECM, which has a high water content as a result of the hydrophilic properties of these elements. Once these chondroblasts become ensconced within the ECM, they are referred to as chondrocytes. In contrast to other tissues within the body, cartilage is avascular and devoid of nerves and lymphatic channels. Because of this relative lack of blood and nutrient supply, the repair process of damaged cartilage can be quite prolonged if not impossible.

Articular cartilage, along with subchondral bone, meniscal fibrocartilage, tendons, ligaments, and synovial fluid comprise the synovial joint. Collectively, these elements are responsible for maintaining joint mobility. Joint instability and degradation resulting from damage to any of these components of the joint space can result in worsening pain and functional disability. Given the advent of space tourism, as well as discussions regarding human travel for longer-distance missions including those to Mars, more research is needed to determine the musculoskeletal risks posed to travelers. The purpose of this review is to evaluate the effects of space and microgravity on hip and knee articular cartilage, including its impact on joint mobility and functional status.
Table I
Summary of findings in the literature on hip and knee cartilage in space microgravity

<table>
<thead>
<tr>
<th>Title</th>
<th>Authors</th>
<th>Year Published</th>
<th>Study Design</th>
<th>Population Characteristics</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spaceflight-Relevant Challenges of Radiation and/or Reduced Weight Bearing Cause Arthritic Responses in Knee Articular Cartilage</td>
<td>Wiley et al.</td>
<td>2016</td>
<td>Prospective cohort</td>
<td>60 rats exposed to hindlimb unloading via tail suspension in modeled zero-gravity environment</td>
<td>Acute degenerative and pre-arthritic changes in the knee articular cartilage was noted on MRI.</td>
</tr>
<tr>
<td>Long-Duration Space Flight and Cartilage Adaptation: First Results on Changes in Tissue Metabolism</td>
<td>Niehoff et al.</td>
<td>2016</td>
<td>Experimental</td>
<td>10 astronauts aboard the International Space Station had pre- and post-flight blood samples taken</td>
<td>Cartilage oligomeric matrix protein found to be increased upon return to Earth.</td>
</tr>
<tr>
<td>Ultrasound Evaluation of the Site-Specific Effect of Simulated Microgravity on Articular Cartilage</td>
<td>Wang et al.</td>
<td>2010</td>
<td>Prospective cohort</td>
<td>6 rats underwent tail suspension for four weeks</td>
<td>Ultrasonography found degeneration of cartilage at the medial femoral condyle and patella.</td>
</tr>
<tr>
<td>Exercise Countermeasures for Knee and Hip Joint Degeneration during Spaceflight</td>
<td>Wiley et al.</td>
<td>Ongoing</td>
<td>N/A</td>
<td>Mice flown in space for 13 days</td>
<td>Preliminary data shows meniscal and soft tissue degeneration.</td>
</tr>
<tr>
<td>Study on the Development of Methods to Produce Artificial Cartilage</td>
<td>Stamenkovic et al.</td>
<td>Ongoing</td>
<td>N/A</td>
<td>Exposure of pig chondrocytes to microgravity in space</td>
<td>Decreased extracellular matrix and increase collagen type I and II. Cellular spacing was also observed.</td>
</tr>
</tbody>
</table>

## Materials and Methods

### Search strategy
This literature review was structured to adhere to PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines. A literature search was conducted to assess English-language reports indexed in PubMed and Google Scholar from 1990 to 2018. The terms “joints,” “joint mobility,” “articular cartilage,” “knee,” “hip,” “space,” “microgravity,” “osteoarthritis,” and variations thereof were utilized. A recent literature review by Ramachandran et al., concerning the effects of spaceflight on spinal physiology, provided a framework for the construction of this literature review on the hip and knee.1

### Selection criteria
The inclusion criteria included any human or animal studies relevant to hip or knee cartilage in space or simulated microgravity conditions. The exclusion criteria were to remove any case reports, reviews, studies examining only oseous physiology, or non-English articles. Furthermore, any reports that had incomplete author information or lacked descriptions of their study design were excluded. In vivo murine studies comprised the majority of the literature.

### Manuscript review
Two authors reviewed all articles from the literature search and subsequently accessed the full manuscripts or monographs of studies that were included in this review.

### Data extraction
The method of data extraction and computation followed the approach outlined by the Cochrane Handbook for Systematic Reviews of Interventions. Given the paucity of literature, heterogeneity in study designs, and variability in selected outcomes, a meta-analysis was not possible.

### RESULTS

#### Eligibility
The literature search yielded a total of 700 citations from PubMed and 1,700 citations from Google Scholar. Following the removal of over 500 duplicates and screening by eligibility criteria, five articles were analyzed, with the summaries of relevant findings shown in Table I.5-10 Of note, one ongoing study which reported preliminary data was included.

#### Responsiveness of cartilage to gravity and weight bearing
As shown by Willey et al., weight bearing and loading effects the mechanically-sensitive cartilage of the knee joint as demonstrated by the reduction in glycosaminoglycan (GAG) content in the hindlimb of unloaded rats, akin to spaceflight, in comparison to normal ground weight-bearing rats.6 Additionally, matrix metalloproteinase-13 protein (MMP-13), which plays a role in collagen type II degradation, was increased. Subsequent return to weight bearing recovered the effects on cartilaginous degeneration to some extent. This study demonstrated the mechanically-responsive nature of cartilage and implicated chondrolysis as a pathogenetic process seen in space and microgravity conditions. Of note, this study did not truly
have the specimens in zero gravity but was rather a study of unloading the rats hindlimbs in an attempt to translate to zero gravity.

Additionally, Niehoff et al. conducted a novel human study, which evaluated the gait of astronauts who orbited the Earth aboard the International Space Station (ISS). In this pilot study, human cartilage exposed to long-term microgravity conditions will be assessed via magnetic resonance imaging (MRI) before and after spaceflight. Additionally, urine markers will also be assessed for changes in cartilage biomarkers.

With regard to animal research, Wang et al. conducted a study that utilized site-specific ultrasound biomicroscopy of rats subjected to simulated microgravity by tail suspension. The medial femoral condyle and patella exhibited significant decreases in articular cartilage thickness as well as an increase in roughness at the patella. Therefore, the knee may have a predilection for cartilaginous injury from microgravity due to the fact that it is a highly loaded joint under terrestrial conditions. A limitation of this study was that the rats were only exposed to simulated microgravity for a total of four weeks.

Sequelaes of cartilage loss

A study conducted by Willey et al., in conjunction with NASA, found that soft tissue damage in the knee and hip can occur with reduced loading, which implicates possible sequelae of decreased cartilage from spaceflight.

The study by Willey and Smith demonstrated that reduced loading can also lead to the degradation of ligaments and menisci of the knee, posing a risk for subluxation or dislocation. In this way, cartilaginous injury from space microgravity exposure can lead to numerous sequelae associated with destabilization and reduced integrity of the hip and knee joint.

Data from murine and human studies demonstrated variable outcomes. For example, although Niehoff et al. showed an increase in COMP in astronauts following return to Earth after a long spaceflight of five months, basic science studies in murine models found conflicting results with different levels of cartilage recovery, as measured by other biomarkers.

Gait in space is known to be altered, with accompanying disruption of the vestibular pathways to the thalamus and cortex. Experiments on murine gait and limb movement patterns in space aboard the ISS are forthcoming and are theorized to correlate with the extent of cartilaginous injury. Devices such as the DigiGait (Mouse Specifics, Inc., Framingham, Massachusetts), which is designed for mice in space, can be modulated for human use and may provide feedback to astronauts on gait and biomechanics to maintain joint mobility and to slow cartilage loss.

Prophylactic measures have been investigated to counter these effects of zero-gravity, with exercise as a known and validated countermeasure to improve hyaline articular cartilage composition, especially of the hip and knee. Astronauts are routinely expected to exercise in space and, by increasing loads on joints in space, may stimulate recovery to normal composition. Other prophylactic measures may involve pharmacologic interventions, such as recombinant human fibroblast growth factor 18 (FGF-18), which is a type of human fibroblast growth factor that has been shown to stimulate cartilaginous growth in preliminary trial results. Over the counter supplements, like glucosamine sulfate, hyaluronic acid, piascledine avocado, and soybean oil extract, are controversial, but many patient accounts indicate they may reduce the pain and inflammation associated with cartilage loss and osteoarthritis.

Further research on these compounds can provide insight on their utility in patients both in space and on Earth.

Cartilage implants and recovery of last cartilage

Engineered cartilage xenografts exposed to a random positioning machine represents an additional technique to combat cartilage loss. At NASA, Stamenkovic et al. are developing a suitable porcine cartilage implant with properties suitable for space travel. After flying pig chondrocytes in space, Stamenkovic et al. observed a decrease in extracellular matrix gene expression and an increase in collagen type I and II, compared to normal chondrocytes.

Additionally, the introduction of clustered regularly interspaced short palindromic repeats (CRISPR) and viral vectors for gene therapy open a promising path for recovering lost cartilage. Although these techniques remain in their infancy, the possibility of inducing cartilage growth in vivo may coincide with developments in long-term space travel.

Consideration for gait assessment in microgravity

Quatman et al. established how altered gait is associated with differential cartilaginous recovery of the knee in patients following surgery. Furthermore, it is known that biomechanics impact skeletal cell behavior to ultimately affect joint behavior.

DISCUSSION

This literature review confirmed the marked paucity of literature assessing the impact of microgravity exposure on hip and knee cartilage. Only five studies were published this decade on the topic of space microgravity and cartilage, one of which is ongoing with no published results. Only one article assessed human subjects and the remaining three were murine. Terrestrial studies should provide the backbone for space and microgravity studies. There remains insufficient data on the use of prophylactic drugs to avoid cartilage degeneration, as well as the role of gene therapy. These methods will inevitably be utilized on space-specific conditions and can improve the treatment of osteoarthritis and other degenerative joint diseases in weight-bearing conditions.

Discussion
study, which was identified in this review, international efforts to remedy this knowledge gap are underway. The future of research on space microgravity conditions as it pertains to hip and knee cartilage appears promising. However, we must look to expand these studies and standardize their methods in an effort to have the ability to apply these results to human subjects. Future questions to be addressed include areas such as the pathophysiology of cartilaginous degradation, the quantification of gravitational force required for adequate cartilage survival, and the effects of space-related radiation on cartilage repair.

**CONCLUSION**

Space and associated microgravity conditions may adversely impact articular cartilage as demonstrated in human and animal studies. The pathogenetic process appears to be due to the mechanically responsive nature of cartilage, which results in increased cartilage metabolism. However, there is insufficient data in the available literature to draw any significant conclusions that quantify or estimate the true impact of microgravity on cartilage health and further investigation is merited. Studies assessing the gravitational force necessary for adequate cartilage survival, the impact of space-related radiation on cartilage repair, and feasible therapeutic options are needed. Further studies may assess pharmacologic interventions, such as recombinant human fibroblast growth factor to stimulate cartilaginous growth and xenograft applications.

**AUTHORS’ DISCLOSURES**

The authors have no conflicts of interest to disclose.