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Staying within the Envelope of Function: Both Joint Overloading and Under-Loading can be Detrimental to Cartilage Health Early after Acl Reconstruction

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Abstract

Purpose: *Under/over-loading following anterior cruciate ligament reconstruction (ACLR) have been reported to affect postoperative cartilage. Conflicting rehabilitation programs promote joint loading at different time points. The purpose of this review was to determine whetherunder/overloading is associated with imaging/biochemical biomarkers of cartilage degradation after ACLR and whether these associations are time-dependent.*

Methods: *PubMed literature search was conducted identifying ACL-reconstructed patients, knee joint moments/vertical ground reaction forces, and imaging or biochemical biomarkers of cartilage degeneration. Initial search produced 357 publications. Fifteen studies (510 patients) published between 2016-2021 satisfied inclusion criteria. Method of cartilage degeneration measurement, whether under/over-loading was associated with cartilage degradation, and time points were assessed.*

Results: *Three studies reported underloading, while two studies reported overloading, was associated with cartilage degradation. Between 18-months and 8-years after ACLR, overloading was consistently associated with degenerative cartilage changes on MRI/ultrasound (7/7 studies).*

Two studies reported under-loading two years or later after ACLR was associated with increased plasma biomarkers of cartilage degradation. While underloading compared to the contralateral limb was associated with serum/plasma cartilage biomarkers at later time-points, it remains unclear if systemic biomarkers are evidence of increased cartilage remodeling in the involved or uninvolved limb.

Conclusion: *Under/over-loading 6-months after ACLR were associated with biomarkers of cartilage degradation, whereas overloading was more consistently associated with imaging biomarkers of cartilage changes 18-months after ACLR. The ineffectively-rehabilitated knee continues to threaten joint health, and current results suggest rehabilitation strategies are needed 28 to promote optimal early postoperative loading while avoiding overloading 18 months after ACLR.*

Level of Evidence: *Level II*

Keywords: Knee, Acl Reconstruction, Loading, Joint Loading, Cartilage, Cartilage Degradation, Rehabilitation, Knee Rehabilitation.

Introduction

The anterior cruciate ligament (ACL) is one of the most common knee ligaments injured, having a reported incidence of 68.6 per 100,000 [12]. For many patients, ACL injury initiates the progression to post-traumatic osteoarthritis (PTOA), with 36% having symptomatic andradiographic changes within ten years after injury [9]. The relative magnitude of joint loading has been reported to influence cartilage changes after ACLR but there is currently no consensus as both under and overloading the joint after ACL reconstruction have been associated with early postoperative cartilage changes at 6 months' duration utilizing MRI [5, 9]. To complicate matters, different research groups are utilizing different metrics for determining these cartilaginous changes. For example, cartilage has been analyzed at different time intervals in the literature as well as these research groups relying on different modalities for assessing these cartilage changes. Therefore, the purpose of this systematic review was to determine whether relative under/overloading is associated with imaging and/or biochemical biomarkers of cartilage degradation after ACLR and whether these associations are time-dependent. We hypothesized that both under and overloading the joint after ACL reconstruction will result in degenerative changes to the cartilage and we expect these changes to be time dependent.

Materials and Methods

This study utilized Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines to complete a comprehensive literature review through PubMed, whereby specific search items were input to identify potential research papers of interest pertaining to patients with ACL reconstruction. Articles were identified using specific keywords and utilizing the phrase: (ACL reconstruction OR anterior cruciate ligament reconstruction) AND (moment OR force OR load OR impulse OR biomechanics*) AND (cartilage OR MRI OR biomarker OR serum OR plasma OR urine OR urinary) NOT (cadaver OR review) AND English language. In addition to using the aforementioned phrase during the literature search, filters were set to Humans and English. This literature search was conducted through PubMed on Thursday, March 17, 2022 during the time of 10:04:53. Inclusion criteria were: 1) studies with patients who underwent ACL reconstruction, 2) knee joint moments and/or vertical ground reaction forces were reported, and 3) at least one biomarker of cartilage degeneration was reported including either imaging biomarkers (magnetic resonance imaging (MRI) or ultrasound) and/or either synovial fluid or peripheral biomarkers of cartilage degradation (serum, plasma, and/or urine). The initial search produced 357 publications for consideration. A title review narrowed the field to 107 possible studies. An abstract and manuscript review identified 15 studies that satisfied the inclusion criteria, as shown in fig. 1. We examined these 15 studies, recording the method of cartilage degeneration detection, whether increased or decreased joint loading was associated with imaging and biochemical biomarkers of cartilage degradation, and the time point when joint loading cartilage changes were assessed. Relative underloading was defined as either vertical ground reaction forces and/or knee joint moments of the operative limb that were less than those reported of the uninvolved contralateral limb. Relative overloading was defined as either vertical ground reaction forces and/or knee joint moments of the operative limb that were greater than those reported of the uninvolved contralateral limb.

Table 1 : Study Demographics

STUDY CHARACTERISTICS	RESULTS	STUDIES RE (%)
MEAN # PATIENTS	34	15 (100)
MEAN % MALES	51	14 (93)
MEAN AGE	27.7	14 (93)
MEAN FOLLOW-UPS MONTHS	1.3	15 (100)
MEAN MINORS COMPARATIVE (N,MAX)	22.5 (10,24)	
MEAN MINORS NON-COMPARATIVE (N,MAX)	14.4 (5,16)	
REPORTED RADIOLOGIC MEASURES		12 (80)

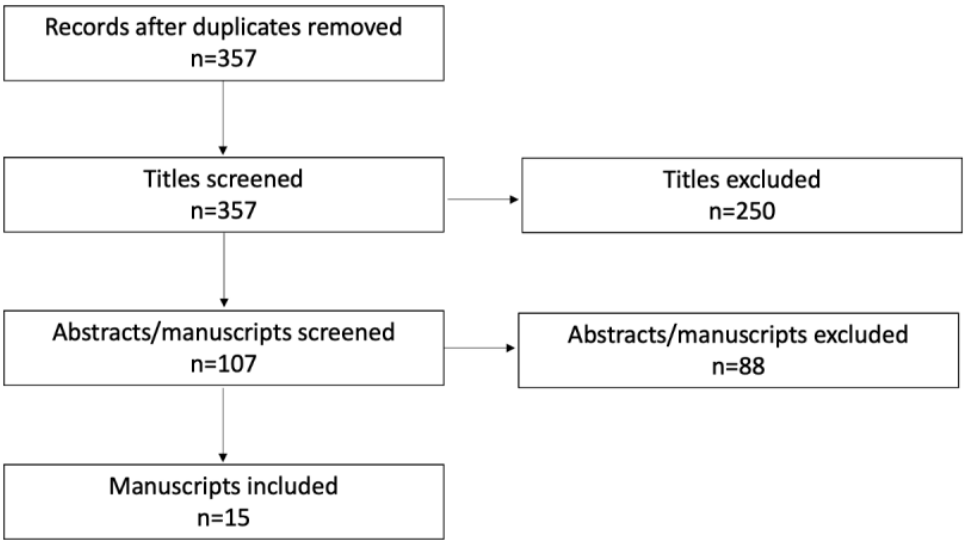


Figure 1: PRISMA Flow Diagram: Diagram demonstrating the identification, screening, eligibility, and final inclusion of manuscripts utilized for this systematic review.

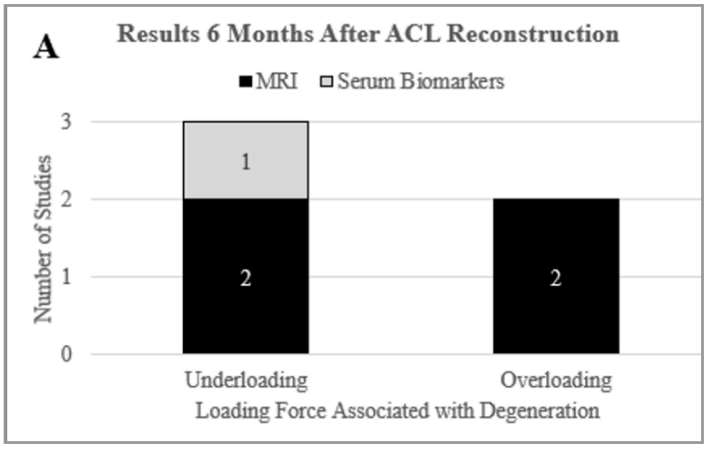
Quality Assessment

Following the selection of studies using our criteria described above, the Methodological Index for Nonrandomized Studies (MINORS) tool was utilized for evaluation of the quality of the included non-randomized studies [15]. The MINORS tool utilizes 12 factors rated on a scale of 0-2, with each variable described as follows: 0 as not reported, 1 as reported but inadequate, or 2 as reported and adequate for evaluation of study quality. Included studies for quality assessment were independently assessed by two authors (DH and SB), and any disagreements were resolved by arbitration and consensus.

Results

Following the selection of manuscripts using the inclusion criteria mentioned above, 15 studies were selected as part of our final analysis for a total of 510 patients. The study characteristics, included below in table 1, demonstrated the following characteristics: mean number of patients included in each study 34, with 100 percent of studies reporting. Mean percentage being male was 51 percent, with 14 studies reporting. Mean age of 27.7, with 14 studies reporting. Mean number of follow-ups assessed in data representation was 1.3, with 15 studies reporting, and included intervals of 3 months, 6 months, 12 months, or greater than 18 months. Mean MINORS score for comparative studies was 22.5, with 10 studies represented and a max MINORS score of 24. Mean MINORS score for non-comparative studies was 14.4, with 5 studies represented and a max MINORS score of 16. 12 out of the total 15 studies reported radiological data for assessment of cartilage outcome. MRI was most often used to assess cartilage degradation, which included 11 of the 15 studies and 418 of the 510 patients. Second most often used to assess cartilage degradation was a serum or plasma biomarker, with 3 of the 15 studies reporting use, for a total of 67 patients. Third most often used to assess cartilage degradation was ultrasound, with 1 study reporting use, for a total of 25 patients represented. In both crosssectional and longitudinal studies, there was no clear trend in whether cartilage degradation was associated with relative under vs. overloading in the early postoperative period. 3 out of 15 studies reported underloading was associated with cartilage degradation, whereas 2 of the 15 studies reported that overloading was associated with cartilage degradation. One study reported no association. On the contrary, much more consistent results were seen at later time points, which is represented as greater than 18 months in table 2 and fig. 2. Between 18 months and 8 years after ACL reconstruction, overloading was consistently associated with degenerative cartilage changes when using either MRI or ultrasound imaging biomarkers (7/7 studies, 287 patients). Two studies, for a total of 49 patients, reported that decreased joint loading two years or later after ACL reconstruction was associated with increased serum and/or plasma biomarkers of cartilage degradation. While underloading compared to the contralateral limb was associated with serum and plasma cartilage biomarkers at later time points, it remains unclear if systemic biomarkers are evidence of increased cartilage remodeling in either the involved or uninvolved limb.

	3 mo		6 mo		12 mo		18+ mo		
Author	Negative Effect	Cartilage Outcome	Negative Effect	Cartilage Outcome	Negative Effect	Cartilage Outcome	Negative Effect	Cartilage Outcome	N
Williams 2021 [20]							Over	MRI	80
Capin 2020 [1]	No Association			MRI					26
Erhart-Hledik 2019 [2]							Over	MRI	17
Pamukoff 2018 [8]							Over	US	25
Shimizu 2019 [14]			Under					MRI	31
Pfeiffer 2019 [9]			Under	MRI					29
Luc-Harkey 2018 [6]							Under	Serum	30
Saxby 2019 [13]							Over	MRI	100
Williams 2018 [21]							Over	MRI	36
Titchenal 2018 [18]							Over	MRI	20
Kumar 2018 [5]			Over	MRI		No effect-MRI			37
Teng 2017 [17]			Over					MRI	33
Pietrosimone 2017 [11]			Under	Serum					18
Pietrosimone 2016 [10]							Under	Serum	19
Kumar 2014 [3]							Over	MRI	9



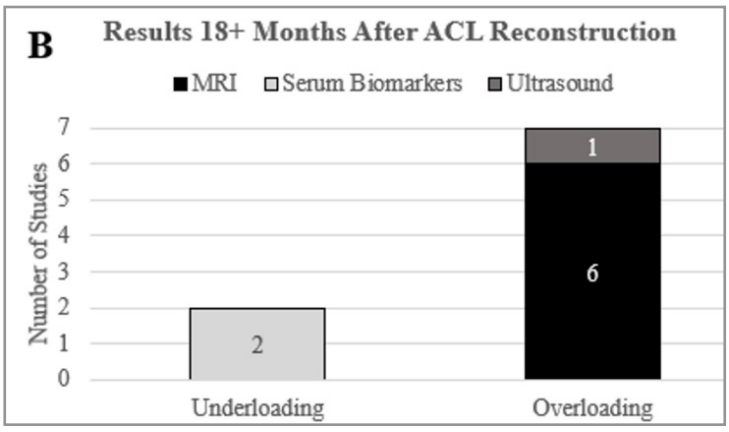


Figure 2: Loading Force and Cartilage Outcome: Visualization representing the loading force associated with cartilage degeneration organized in a time-dependent fashion, with fig. 2A depicting results 6 months following ACLR and fig. 2B depicting results 18+ following ACLR. Additionally, these results are visually differentiated using color for each measurement modality (serum as light gray, MRI as black, and US as dark gray).

Discussion

We hypothesized that both under and overloading of ACL reconstructed knees would be associated with cartilage degeneration, and that these degenerative effects would be time dependent. The results partially supported our hypotheses and suggest that the influence of relative over vs. underloading on imaging and biochemical biomarkers of cartilage changes appears to differ based on time after reconstruction. Within 6 months of surgery, there is no clear trend between the relative magnitude of joint loading on cartilage degeneration. At this time point, 3 studies reported underloading to be associated with degeneration [9, 11, 17]. Two of these studies used MRI to monitor changes in cartilage [9, 17], while 1 utilized serum biomarkers [11]. At this same time, 2 additional studies that utilized MRI found overloading to be associated with degeneration [5, 17].

One study found no association between joint loading and cartilage changes in the early postoperative period after ACLR [1]. With such divided results, there can be no clear consensus as to whether under vs. overloading may increase early cartilage changes within the first 6 months after ACLR. Perhaps there is no definitive answer and put simply there may be a "sweet spot" of loading during these 6 months, but additional research in this area is needed.

However, as time progresses to 18 months and beyond following surgery, the results become more consistent. Seven studies found overloading to be associated with degenerative changes [2, 3, 6, 13, 18, 20, 21]. While 2 studies found underloading to be associated with cartilage degeneration 18 months or more after ACLR [6, 10]. Interestingly, the method used to monitor this cartilage degradation is clearly demarcated by the results found: the two studies associating underloading with cartilage degeneration utilized serum biomarkers [6, 10]. Whereas the seven studies finding overloading to be associated with cartilage degeneration utilized imaging biomarkers (6 used MRI [3, 13, 18 , 20, 21]. and 1 used ultrasound to assess changes) [8]. MRI and ultrasound methods may be more direct in assessing degeneration of the cartilage in the ACLR knee, whereas serum biomarkers may be a poor representation of the intraarticular environment – especially at later time points [3, 20]. Based on these results, it would appear that overloading is associated with degenerative changes at 18 months and beyond after ACLR.

These differing methods of measuring cartilage degeneration is one of the largest limitations of this study and generates significant heterogeneity. When it comes to serum biomarkers specifically, it is difficult to know if the markers of inflammation and/or cartilage degradation are truly from the reconstructed knee, or if they are from other sources in the body. In theory, increased systemic biomarkers of cartilage degradation could be from the contralateral, healthy knee, that may be subject to overloading if the reconstructed knee is underloaded. This lack of specificity clouds the results and leads to variations across studies. However, when looking at studies that used MRI, it is noteworthy that at 18 months and beyond they are all in concordance with overloading being detrimental to cartilage health in reconstructed knees. As MRI can image and measure cartilage in the reconstructed knee, it is considered the gold standard in assessing early PTOA changes. So, while imaging and biochemical biomarkers show differing results, the MRI studies can be interpreted with higher confidence due to the current opacity of serum biomarkers and their indirect evaluation of the cartilage in reconstructed knees [19].

In conclusion, before making concrete guidelines and recommendations, future studies need to be performed with a standardized method of measuring cartilage degeneration in ACL reconstructed knees. It is likely that this method should be MRI, as serum biomarkers are currently too indirect to be definitive. The existing results found and assimilated in this paper suggest that in the 6 months following surgery there appears to be a "sweet spot" of load on the knee that prevents cartilage degeneration. Both under and overloading during this time period were found to have negative effects on cartilage. However, at 18 months and beyond, the studies using MRI all found overloading to be associated with cartilage degeneration in the ACLR knee. There appears to be an intricate balance that is dependent on time to optimize joint health during rehabilitation from ACL reconstruction.

Conclusion

Both relative under and overloading 6 months after ACLR were associated with biomarkers of early cartilage degradation, whereas overloading was consistently associated with imaging biomarkers of cartilage changes 18 months or more after surgery. The ineffectively rehabilitated knee continues to threaten long-term joint health, and the current results suggest rehabilitation strategies are needed to promote optimal loading in the early postoperative period while also avoiding overloading 18 months or more after ACLR.

Conflict of Interest

none

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Ethical Approval

n/a

Informed Consent

n/a

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