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Association between gait biomechanical changes after anterior cruciate ligament injury or reconstruction and the development of osteoarthritis: systematic review and meta-analysis protocol

Matteo Campion, PT[1,2], **Jérôme Riera, PT** [1,3], **Alexandre JM. Rambaud, PT, PhD** [3,4], **Tomas Néri, MD, PhD**[4,5] **and Noémie C. Duclos, PT, PhD** [1,6]

[1]Université de Bordeaux, Collège Sciences de la santé, IUSR, Bordeaux, France , [2]Physiotherapy School of Bordeaux, University Hospital of Bordeaux, Bordeaux, France, [3]Université Jean Monnet Saint-Etienne, Lyon 1, Université Savoie Mont-Blanc, Laboratoire Interuniversitaire de Biologie de la Motricité, F-42023, Saint-Etienne, France, [4]Physiotherapy School of Saint-Etienne, Campus Saint Michel, Saint-Etienne, France, [5]Department of Orthopaedic Surgery University Hospital of Saint Étienne, Saint-Etienne, France, [6]Université de Bordeaux, INSERM, BPH, U1219, Bordeaux, France

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ABSTRACT

Background: Anterior cruciate ligament injuries and their reconstruction have been shown to increase the risk of developing knee osteoarthritis. Several studies have investigated the association between gait biomechanics and early cartilage changes. Given the burden of osteoarthritis, it may be important to better understand factors that increase the risk of developing osteoarthritis following anterior cruciate ligament injury and/or reconstruction. **Objective**: This paper presents the protocol for a systematic review and meta-analysis aimed at evaluating the existing literature on the relationship between biomechanical changes in gait following anterior cruciate ligament injury or reconstruction and the early onset of osteoarthritis. **Methods**: An electronic literature search will be conducted using the following electronic databases: MEDLINE, WEB OF SCIENCE, CINAHL, and SPORTDiscus. Studies published in English and French will be included if they investigate the association between biomechanical changes in gait following anterior cruciate ligament injury and/or reconstruction and the early onset of osteoarthritis, as assessed by biological markers or imaging criteria. Methodological quality will be assessed using the Downs And Black modified checklist. If there is sufficient homogeneity in the outcomes across studies, a meta-analysis will be carried out. **Conclusion**: This will be the first systematic review to summarise the existing data on the association between biomechanical changes in gait following anterior cruciate ligament injury and/or reconstruction and the early onset of osteoarthritis, as assessed by biological markers or imaging criteria.

KEYWORDS: anterior cruciate ligament, ACL injuries, ACL reconstruction, biomechanical phenomena, gait, osteoarthritis

Background

In the United States, approximately 80,000 anterior cruciate ligament (ACL) injuries are reported annually [1]. In a sports population, the incidence rate of ACL injuries is 1.5 injuries per 10,000 athletic exposures in women and 0.9 per 10,000 athletic exposures for men, with the highest incidence observed in pivoting sports such as soccer, football, or basketball [2, 3]. ACL injuries are treated either by conservative treatment or by surgical reconstruction of the ligament (ACLR) [4]. ACL injury management aims to restore knee function, manage psychological consequences, prevent further knee injury and osteoarthritis (OA), improve long-term quality of life, and return athletes to their pre-injury performance levels [5]. However, the likelihood of developing knee OA is eight times greater for individuals who undergo surgical reconstruction or conservative treat-

Corresponding author: Matteo Campion, Université de Bordeaux, Collège Sciences de la santé, IUSR, Bordeaux, France.
e-mail: campion.m@outlook.fr

ment compared to the general population [6].
The causes of early development of knee OA following ACL injury or ACLR are likely multifactorial, but gait biomechanics is often cited as a contributing factor [7, 8, 9].
There is evidence that gait biomechanics (e.g., knee extension moment, knee excursion) are altered after ACL injury or ACLR compared to healthy individuals [10, 11, 12]. Indeed, these conditions alter the interaction between the bony anatomy, articular surfaces, ligaments, menisci, and surrounding musculature, potentially modifying the loads and functional demands placed on healthy structures, as well as altering knee joint biomechanics [13]. Some studies have shown that biomechanical changes in gait following ACL injury or ACLR may be associated with accelerated degradation of the composition and metabolism of the articular cartilage of the knee [14, 15, 16].
However, the mechanisms underlying the early development of OA are still poorly understood, and it remains unclear whether alterations in gait biomechanics lead to long-term degeneration of knee cartilage [11, 12].
Several authors have investigated this relationship between changes in knee biomechanics following ACL injury and/or ACLR and the development of OA using imaging (e.g., MRI) or biology. Variations in knee joint moment during gait after ACLR have been associated with alterations in knee cartilage thickness measured by MRI at the knee joint [9, 17]. There are also studies that have observed an association between biomechanical gait alterations following ACLR and an increase in biomarkers of cartilage breakdown such as cartilage oligomeric matrix protein (COMP) [18].
To our knowledge, no systematic review of these studies has examined the association between biomechanical changes during gait following ACL injury and/or ACLR and the onset of knee OA. Given that OA remains a significant economic and humanistic burden [19], it is important to better understand factors that increase the risk of developing OA following ACL injury and/or reconstruction.
The results of this review could have significant implications for clinical practice and the management of ACL injury and ACL reconstruction. Integrating biomechanical gait analysis into rehabilitation protocols could allow personalised treatments, optimise clinical decisions, and reduce the risk of developing OA and other long-term consequences for individuals.

Objective

The aim of our systematic review is to summarise the existing literature and perform a meta-analysis of the associations between biomechanical gait variables and cartilage changes leading to the development of OA following ACL injury or ACLR. To this end, we will answer the following PICO question: Are biomechanical changes during gait following ACL injury or ACLR associated with markers of the onset of OA in the injured knee, compared with the contralateral knee or healthy controls?

Methods

This protocol follows PRISMA-P guidelines, and the review will follow PRISMA guidelines. PRISMA-P provides a structured format for reporting protocols of systematic reviews and meta-analyses [20]. PRISMA provides guidelines for reporting the results of systematic reviews and meta-analyses [21].

Eligibility criteria The eligibility criteria are based on the PICOS elements of our question and are described in Table 1.

Only adults will be included as their musculoskeletal system is fully developed. Individuals having undergone an ACLR and those who have received conservative treatment will be included in the study. This will allow us to investigate the relationship between biomechanical changes during gait and the onset of OA in different clinical contexts, broadening the scope of our review. There will be no restrictions on surgical technique, time since injury or surgery, or sex, to increase the generalisability of our findings.

Individuals with other musculoskeletal conditions or neuromuscular diseases will be excluded to ensure that the biomechanical changes are primarily related to the ACL injury regardless of whether or not it was treated conservatively. To eliminate confounding factors, studies that do not distinguish between simple ACL injury and ACL injury associated with a meniscal tear or ACLR with or without meniscal surgery, will be excluded [22].
We will include studies that compare data from the injured lower limb with the contralateral uninjured lower limb or with a control group of healthy individuals. This will help to identify changes beyond normal variation that highlight specific consequences of ACL injury and/or reconstruction. To be included, the control group and the injured group should be comparable in terms of physical activity levels and body mass index, two variables that may also influence the development of OA [23].
Studies will be included if the outcome focuses on changes in cartilage, assessed using biological markers, imaging, or other objective markers. This will allow for the investigation of the association between alterations in gait biomechanics following ACL injury or reconstruction and the emergence of knee OA [24, 25, 26].
This review will include studies employing experimental or observational designs, with the main objective of testing the association between gait biomechanics and the onset of knee OA (e.g., cohort studies, cross-sectional studies, baseline measurements from randomised controlled trials). Other types of literature (see Table 1), will be excluded, as they cannot reliably examine such an association [27].

Information sources The research will be conducted using four electronic databases: MEDLINE (via PubMed), Web Of Science, CINAHL, and SPORTDiscuss (via EBSCOhost).

Search strategy In selected electronic databases, the search strategy presented in Table 2 will be performed. Keywords were selected based on PICO concepts.
In MEDLINE, via PubMed, for the sake of completeness, terminology [MeSH Terms] will be added to the concepts where possible (words in bold in table 2).

Study records Records will be managed using Zotero, reference management software [28].
The records will then be transferred to the free version of Rayyan, an intelligent collaborative research platform for conducting literature reviews and systematic reviews [29]. Duplicates will automatically be eliminated in Rayyan.
Two reviewers (JR, MC) will then independently carry out an initial selection based on the title and abstract of the articles. At this stage, articles will not be included directly, those that could potentially meet our criteria will be classified as "maybe". All other articles will be excluded. Each reviewer will undertake an independent review of all titles and abstracts classified as "maybe" to validate their eligibility for inclusion. Subsequently, the blinding between reviewers will be removed. A meeting will be held between the two reviewers to reach a consensus about the pre-selection list. If a consensus cannot be reached, a third reviewer with experience conducting systematic reviews will be consulted.
The two researchers will independently read the full text of the eligible articles to decide on their final inclusion according to the established criteria. When necessary, a further discussion will be held between the two reviewers to reach a consensus. If a consensus cannot be reached, a third reviewer with experience conducting systematic reviews will be consulted. Ultimately, one reviewer will extract data about demographics, biomechanical evaluation, OA assessment, and the results of statistical analyses from the included studies.

Data items All PICOS items will be sought, such as variables for subject characteristics (age, sex, BMI, level of physical activity, time since injury

Table 1 Eligibility criteria

PICOS	Inclusion criteria	Exclusion criteria
Population	Adult ($\geq$ 18 years). With ACL injury, with or without reconstruction, no restriction on surgical technique, time since injury or surgery, nor sex.	Individuals with musculoskeletal (e.g. bilateral ACL lesion) or neuromuscular diseases that are likely to cause gait changes. No distinction between simple ACL rupture or ACL rupture associated with meniscal tear.
Intervention	All types of knee biomechanical assessment during gait, e.g., joint kinematics, kinetics, ground reaction force (GRF).	/
Comparison	Biomechanics of the healthy contralateral lower limb and/or lower limb from a healthy control group.	No control group (healthy control group or healthy contralateral lower limb).
Outcomes	Changes in cartilage that lead to the onset of OA, or with OA directly using biological markers or imaging techniques.	/
Studies Design	All observational or experimental studies in humans. In English or French. No restriction on publication date.	Literature review. Pilot study. Grey literature. Opinion papers. Congress abstracts.

or reconstruction, associated lesions), biomechanical variables measured at the knee during gait and variables related to the development of knee OA. Information about each study (study design, aim(s), sample size, and publication year) will also be extracted.

Outcomes and prioritisation The outcomes related to the development of OA that will be sought are those observed on X-ray (e.g., narrowing of the tibiofemoral joint), MRI (e.g., relaxation time), other imaging criteria, and biological markers that reflect a change in cartilage metabolism (e.g., C2C:CPII ratio). Outcomes of the biomechanical variables that will be sought include knee joint moments, knee joint excursion, knee joint peak range of motion and ground reaction forces. Results of the statistical analyses testing the association between gait biomechanics variables and the onset of knee OA, as well as whether there is a significant difference between ACL-injured limbs and uninjured/control limbs will be extracted.

Risk of bias in individual studies The Downs and Black modified checklist will be used to assess the methodological quality of randomised and nonrandomised comparative studies [30]. This index is scored out of 28, with higher scores indicating higher-quality studies. However, eight questions from this quality appraisal instrument (questions 4, 8, 14, 15, 19, 23, 24, and 27) do not apply to observational study designs. Additionally, 2 other items (questions 9 and 26) do not apply to studies with a cross-sectional design. If all of the remaining items are evaluated positively, studies with a longitudinal design can be assigned a total score of 20 points, while those with a cross-sectional design can receive 18 points [31]. In our study, studies meeting 60-74% of the applicable criteria will be categorised as moderate quality, those meeting more than 75% will be considered high quality, and those meeting less than 60% will be classified as low quality [32].
The Downs and Black modified quality index will be completed by two reviewers, with discrepancies resolved during a consensus meeting. A third reviewer will check the results.

Data synthesis All data on population characteristics, gait assessment, and variables related to the onset of OA will be collected, summarised in a descriptive manner using tables and graphs, and analysed through a descriptive narrative synthesis.
The inter-rater agreement between investigators will be assessed at each step for study inclusion and methodological quality using Cohen's Kappa coefficient.
To address the association between biomechanical variables and the onset of OA in the injured or reconstructed limbs, the uninjured limbs and in the control limbs, a qualitative synthesis will be carried out to describe, analyse and summarise the body of evidence in the literature. If the variables analysed across the studies are homogeneous, a meta-analysis will be conducted by pooling effect sizes using a random effects model. The presence of heterogeneity in effect sizes will be addressed using the Q value, the degree of freedom, and the corresponding p-value. A significant p-value ($p \leq 0,05$) will indicate that the true effect sizes vary. The variance of the true effects will be estimated using T^2, T being the estimated standard deviation. The computation of I^2 will then inform us about what proportion of the observed variance is real [33]. Several factors may influence the presence of heterogeneity, including the treatment status (e.g., operated or not), the presence of associated lesions (e.g., meniscal lesions), and sex. Analyses using a random effects model with separate estimates of τ^2 for each sub-group will be performed. The time elapsed since the injury or surgery may also influence the presence of heterogeneity in effect sizes. A sensitivity analysis will be conducted to evaluate the influence of the data collection period on the effect size. The specific timeframes under consideration are 0-6 months (mo), 6 mo - 1 year (yrs), and more than 1yr post injury or surgery. These specified timeframes are based on the established timelines for rehabilitation following ACLR. The objective is for individuals to resume their sporting activities between six months up to one year after ACLR [34]. It is possible that radiological changes may take longer to manifest than the typical timescale of one year [35]. Therefore, the analyses will cover a timeframe of more than one year. All analyses will be performed with RStudio software.

Table 2 Search strategy

PICO	CONCEPT	KEYWORDS
p	Anterior cruciate ligament	1. anterior cruciate ligament 2. ACL 3. 1 OR 2
	Injury and/or reconstruction	4. anterior cruciate ligament reconstruction 5. anterior cruciate ligament injur* 6. surgery 7. rupture 8. deficien* 9. insufficien* 10. tear 11. dysfunction 12. OR/4-22 13. 3 AND 12
I	Gait	14. gait 15. walking 16. locomotion 17. OR/14-16
	Biomechanics	18. biomechanical phenomena 19. mechanic* 20. torque 21. mechanical torsion 22. movement 23. moment* 24. angle* 25. rotation* 26. kinetic* 27. kinematic* 28. joint load* 29. ground reaction force 30. OR/18-29 31. 17 AND 30 32. 13 AND 31
C	/	/
O	Osteoarthritis	33. osteoarthritis 34. cartilage 35. disease 36. breakdown 37. thickness 38. degeneration 39. OR/35-38 40. 34 AND 39 41. 33 OR 40 42. 32 AND 41

Publication bias Publication bias will be assessed using a funnel plot.

Confidence in cumulative evidence The strength of the body of evidence will be assessed using GRADE (Grading of Recommendations, Assessment, Development, and Evaluations), a transparent framework for developing and presenting summaries of evidence that provides a systematic approach to making recommendations for clinical practice. GRADE has four levels of evidence: very low, low, moderate, and high. The quality of evidence can be determined after considering the type of studies, the quality of the studies, the homogeneity of the results and the directness of the scientific data [27, 36, 37].

Fundings

None.

Supplementary data

PRISMA-P Checklist.

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