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Review

Osteoarthritis-related biomarkers following anterior cruciate ligament injury and reconstruction: a systematic review

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SUMMARY

Objective: There is an increased risk of developing knee osteoarthritis (OA) following anterior cruciate ligament (ACL) injury. Biomarkers may provide diagnostic, prognostic, or burden of disease indicators of OA before radiographic changes become apparent. Unfortunately, there has been no systematic review to clarify which biomarkers may be most informative following injury. Therefore, this review critically investigated existing studies of OA-related biomarkers in ACL-deficient (ACL-D) and reconstructed (ACL-R) patients to summarize the current evidence and identify knowledge gaps.

Design: A systematic review of the literature in Web of Science and PubMed databases (1960–June 2014) was performed. All English-language case–control and longitudinal studies assessing OA-related biomarkers in ACL-D and ACL-R patients were considered. Data regarding biomarker changes over time within ACL-D and ACL-R patients as well as differences in ACL-D/ACL-R patients compared with a control group were extracted from pertinent studies.

Results: A descriptive summary of 20 included studies was produced. In ACL-D patients compared with controls, synovial fluid biomarkers indicated elevated collagen turnover, while the inflammatory cytokine response was inconclusive. In ACL-R patients, serum concentrations indicated decreased collagen breakdown, but urine concentrations were indicative of greater collagen breakdown when compared to controls. Compared to preoperative values, the overall inflammatory cytokine response measured with synovial fluid biomarkers increased while plasma biomarkers did not change following reconstruction.

Conclusion: Patients with ACL-D or ACL-R have altered biomarkers indicative of OA. More research with standardized reporting is needed to effectively determine which biomarkers are the most indicative for OA development and progression following ACL injury.

Introduction

Anterior cruciate ligament (ACL) injury is one of the most common traumatic knee injuries sustained by relatively young and physically active individuals, with an estimated 250,000[1] ACL injuries and 175,000[2] ACL reconstructions occurring annually in the United States. People with a history of knee injury have between 286%[3] and 495%[4] greater odds of developing knee osteoarthritis (OA) than those who have never sustained a knee injury. It has been hypothesized that an underlying cascade of structural and biochemical changes occurs early following ACL injury, ultimately resulting in the onset of knee OA. In fact, one-third of patients

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sustaining an ACL injury will develop knee OA within the first decade following injury regardless of surgical reconstruction status[5]. Although rapidly progressive knee OA occurs in the majority of ACL injured patients within two decades of injury[5], there is no effective treatment to prevent the development of OA following ACL injury. One key reason for a lack of preventive therapies may be the lack of validated methods to diagnose and monitor early disease[6]. With an estimated $3 billion spent annually on the treatment of posttraumatic OA[7], it is critical that methods be developed to evaluate the presence and progression of early-stage OA following ACL injury or ACL reconstruction (ACL-R).

Understanding factors that lead to the development of posttraumatic OA following ACL injury and ACL-R is important for decreasing the need of future total knee arthroplasty as well as limiting the extent of chronic disability and mitigating the risk of developing inactivity related co-morbid health conditions (e.g., obesity, type II diabetes, cardiovascular disease)[8,9]. Currently, posttraumatic knee OA is commonly diagnosed based on the presence of radiographic signs of the disease and complaints of knee pain[10]. However, radiographic assessments of OA rely on the presence of joint space narrowing and osteophyte formation that are signs of late-stage joint degradation has occurred, but the development of OA possibly originates early following traumatic injury due to a cascade of biochemical and biomechanical events.

The evaluation of biochemical markers (biomarkers) that indicate abnormal joint turnover shortly after injury may be an important tool in understanding and treating posttraumatic knee OA[11]. Biomarker evaluation may provide an effective approach for detecting OA development before significant advancement of the disease. However, a wide range of possible biomarkers has been used to detect early changes in tissue turnover following ACL injury and no consensus on their validity has been reached. This review seeks to systematically evaluate and synthesize studies with case–control and repeated measures designs that evaluate biomarkers related to joint metabolism and joint inflammation in both ACL deficient (ACL-D) and ACL-R patients compared with healthy, matched controls as well as evaluating changes in biomarkers over multiple time intervals. The goals of this review are to highlight the current evidence of biomarker alterations following ACL injury, and to identify potential gaps in the literature to aid in the development of future studies.

Methods

Search strategy

The Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines[12] and a written protocol were followed to conduct an exhaustive systematic, electronic search of the Web of Science and PubMed databases. A reference librarian at the University of North Carolina at Chapel Hill assisted the investigators in performing the search. The following search was performed initially performed on August 12, 2013 and updated on June 9, 2014: ACL AND (blood OR urine OR synovial fluid OR serum OR plasma OR biomarkers). We included studies published since January 1, 1960 that were written in English and used human participants. Bibliographies from all relevant studies found in the initial online search were cross-referenced to identify any other pertinent articles. The definitions for biomarker abbreviations that were used in the individual studies have been included in Table I.

Selection criteria

Our focus was on articles that evaluated wet, or fluid based, biomarkers related to the development of OA (joint metabolism and inflammation) in human ACL-D and ACL-R patients. Three reviewers (MSH, BAL, BP) identified eligible articles if an article met the following criteria: (1) enrolled ACL-D or ACL-R patients; (2) included a control group or multiple time points for between or within group comparisons; and (3) evaluated biomarker change following ACL injury or ACL-R. An article was excluded if: (1) treatment was used specifically in an attempt to alter biomarker concentrations other than standard physical rehabilitation; (2) patients had a revision of previous ACL-R; or (3) contralateral knee biomarker concentrations were used as control group due to concerns about systemic alterations in biomarker concentrations following injury, as well as potential aberrant gait kinematics of the contralateral knee affecting biomarker concentrations.

Table I
Biomarker abbreviations

BMP	Bone morphogenic protein
BSP	Bone sialoprotein
C12C	Collagen type I and II cleavage product
C2C	Collage type II cleavage product
COMP	Cartilage oligomeric matrix protein
CTX-II	C-terminal cross-linked telopeptide of type II collagen
CPII	Procollagen II C-propeptide
CRP	C-reactive protein
CS846	Aggrecan Chondroitin Sulfate 846 epitope
GM-CSF	Granulocyte-macrophage colony-stimulating factor
HA	Hyaluronic acid
IFN-γ	Interferon-gamma
IL	Interleukin
IL-1ra	Interleukin-1 receptor antagonist
MCP-1	Monocyte chemotactic protein-1
MIP-1β	Macrophage inflammatory protein-1 beta
MMP	Matrix metalloproteinase
NO	Nitric Oxide
OPN	Osteopontin
PDGF	Platelet-derived growth factor
TIMP	Tissue inhibitor of metalloproteinase
TGF-β	Transforming growth factor-beta
TNF-α	Tumor necrosis factor-alpha
VEGF	Vascular endothelial growth factor
WF6	Chondroitin sulfate epitope

Methodological quality assessment

The Critical Appraisal Skills Programme (CASP)[13] was used to evaluate the literature for: (1) clarity and preciseness of overall results of the study; (2) the validity of the results of the study; and (3) relevance of the results of the study. The CASP score for case control studies ranges from 0 to 11 points (11 = highest quality), and the CASP score for longitudinal studies ranges from 0 to 12 possible points (12 = highest quality; Tables II and III). Three authors (MSH, BAL, BP) independently rated each included article and awarded a total point value to each study. If there was a discrepancy between the points awarded, the three authors discussed differences and achieved a unanimous consensus regarding study inclusion.

Data extraction

A standardized data extraction form was created by MSH and reviewed and edited by BP. Two investigators (MSH and BAL) extracted the type of biomarker (e.g., collagen breakdown, collagen synthesis, pro-inflammatory cytokine), biomarker names, publication year, ACL status (deficient or reconstructed), age and sex of patients and controls, time since injury, time between injury and surgery, concomitant knee injury, fluid sample (e.g., synovial fluid, blood), assay analysis technique, and mean/median and standard deviation/quartile values for biomarker levels by patient and control group.