Serum Cartilage Biomarkers and Shoulder Instability

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Abstract

Differences in cartilage biomarkers have been noted in patients with anterior cruciate ligament tears, but little is known about any similar relationship with shoulder instability. This study evaluated the relationship between serum cartilage biomarkers and shoulder instability. The authors present a prospective cohort study of young athletes followed from 2006 to 2010. A nested case-control analysis was conducted within this cohort to evaluate the association between preinjury collagen type II cleavage (a marker for type II collagen cleavage) and procollagen II carboxy propeptide (a marker of cartilage synthesis) and the subsequent likelihood of shoulder instability during the 4-year follow-up period. Preinjury collagen type II cleavage and procollagen II carboxy propeptide levels in 51 subjects who had shoulder instability were compared with levels in 210 subjects without documented anterior cruciate ligament or shoulder instability (control group) with commercially available enzyme-linked immunosorbent assay kits. Mean preinjury collagen type II cleavage levels in patients who subsequently had shoulder instability were significantly lower than those in the control group (73.91 vs 79.24 pg/mL, \(P=0.03\)). No significant difference was found in preinjury procollagen II carboxy propeptide levels compared with the control group (359.94 vs 396.37, \(P=0.24\)). This study is the first to examine the relationship between baseline collagen biomarkers and subsequent shoulder instability. The finding of lower baseline collagen type II cleavage levels in patients with subsequent shoulder instability may represent a genetic predisposition or a compensatory mechanism by which cartilage degradation is decreased in those who are more likely to have instability. [Orthopedics. 2017; 40(1):34-36.]

Shoulder instability is endemic in young athletes and military personnel.\(^1,2\) Most epidemiologic studies of shoulder instability showed that age, sex, and activity level have the greatest effect on primary incidence and recurrence.\(^3,4\) For example, long-term prospective cohort studies found that younger male patients are most predisposed to recurrent dislocation.\(^1\) Similarly, a recent meta-analysis of 10 studies that included nearly 1300 individuals found that male patients younger than 40 years were most likely to have recurrent instability.\(^5\) Although these studies helped to identify epidemiologic risk factors for instability, they did not identify modifiable factors, such as strength, that could be used to prevent instability.\(^6,7\)

Recent work in a cohort of patients with injury to the anterior cruciate ligament (ACL) showed cartilage biomarkers that were associated with ACL injury.\(^8,9\) More
specifically, levels of biomarkers related to type II collagen synthesis (procollagen II carboxy propeptide) and degradation (collagen type II cleavage) decrease after ACL injury. It has been hypothesized that these changes represent a different environment for cartilage metabolism or that they may be a direct result of an altered mechanical profile.

A great deal of research has focused on the biomarker profile after ACL injury, but no studies have examined these biomarkers in the setting of shoulder instability. This study was conducted to identify differences in cartilage biomarkers in a group of patients who had subsequent glenohumeral instability compared with matched control subjects. The authors hypothesized that there would be significant differences in the preinjury cartilage biomarker concentration in subjects with subsequent shoulder instability.

**Materials and Methods**

After institutional review board approval was obtained from the Keller Army Hospital (West Point, New York), a prospective cohort study of young athletes was conducted between 2006 and 2010. All participants were either cadets or active duty military personnel at the United States Military Academy at West Point, New York. Injuries were tracked with the Cadet Injury and Illness Tracking System, and surgical records were tracked with the Surgery Scheduling System. Control subjects were excluded if they had a history of ACL injury, a documented history of shoulder instability, or a history of surgical intervention requiring ligamentous repair of the knee. Control subjects were matched according to 3 baseline characteristics: age (±2 years), height (±2 inches), and weight (±15 pounds).

Of 1050 subjects who provided consent, a preinjury baseline serum sample was available for 994. A nested case-control analysis was conducted within this cohort to evaluate the association between preinjury collagen type II cleavage and procollagen II carboxy propeptide levels and the subsequent likelihood of shoulder instability during the 4-year follow-up period. These 2 biomarkers were selected based on previous work at the study institution that showed the greatest association with risk of ACL injury.

Further, procollagen II carboxy propeptide levels have been directly correlated with type II collagen synthesis, whereas collagen type II cleavage is a cleavage product that is highly specific for type II collagen degradation in articular surfaces. All collagen type II cleavage and procollagen II carboxy propeptide levels were analyzed with commercially available enzyme-linked immunosorbent assay kits (IBEX Technologies, Inc, Montreal, Canada), and tests were run in duplicate.

Independent samples *t* tests were used to compare collagen type II cleavage and procollagen II carboxy propeptide levels in the 51 subjects who had shoulder instability vs 210 matched control subjects. Statistical analysis was performed with STATA version 10.1 software (StataCorp, College Station, Texas). Significance thresholds were set at *P*=.05 before initiation of the study.

**Results**

As was predicted on the basis of matched samples, patients who had shoulder instability were highly similar to the control group. Of the 51 subjects who had a documented episode of shoulder instability, 46 were male and 5 were female. Mean age was 18.4 years. Mean weight was 76.3 kg, and mean height was 175.7 cm. The racial composition of this cohort was 74.5% white, 5.9% black, 2.0% Asian, 9.8% Hispanic, and 7.8% other. In comparison, the control group included 210 subjects, and of these, 177 were male and 33 were female. Mean age was 18.2 years. Mean weight was 73.1 kg, and mean height was 175.9 cm. The racial composition of this group was 76.2% white, 3.8% black, 7.6% Asian, 7.1% Hispanic, and 6.7% other.

**Discussion**

This study is the first known work to evaluate markers of cartilage metabolism in a cohort of subjects with shoulder instability. A significant difference in serum collagen type II cleavage levels was found in subjects with subsequent shoulder instability compared with control subjects. The exact cause of this difference is unknown, but this study provides a foundation for continued work on cartilage markers in shoulder instability.

The vast majority of cartilage biomarker analysis has been conducted in the context of ACL injury. Previous studies found baseline differences in collagen type II cleavage and procollagen II carboxy propeptide levels, but most focused on alterations in

### Table

**Differences in Collagen Type II Cleavage and Procollagen II Carboxy Propeptide Biomarker Concentrations Before Shoulder Instability**

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Control</th>
<th>Shoulder Instability</th>
<th><em>P</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Collagen type II cleavage</td>
<td>79.24±15.24</td>
<td>73.91±19.18</td>
<td>.03</td>
</tr>
<tr>
<td>Procollagen II carboxy propeptide</td>
<td>396.37±199.10</td>
<td>359.94±175.14</td>
<td>.24</td>
</tr>
</tbody>
</table>
biodmarkr levels (or ratios of levels) after ACL injury.\textsuperscript{4} Interestingly, serum collagen type II cleavage levels decrease after ACL injury.\textsuperscript{13,14} This decrease may be the result of a differing cartilage biomarker profile within the articular surface or an altered mechanical profile. These findings imply that a destabilizing ligamentous injury may create a physiologic state in which type II collagen degradation is slowed. In support of this hypothesis, Pietrosimone et al\textsuperscript{14} showed that greater axial loading of the knee joint after ACL reconstruction decreases the rate of cartilage degradation, possibly implicating a projective mechanism by which the body preserves cartilage after ligamentous injury.

Although most studies of biomarkers have been performed in ACL injury, the finding that collagen type II cleavage levels are decreased in subjects with subsequent shoulder instability may imply a protective mechanism that slows cartilage degradation. Because the study cohort had no known previous episodes of shoulder instability, it is unclear how this mechanism could be initiated. One hypothesis is that it occurred through previous episodes of clinically insignificant shoulder instability that did not prompt the subject to seek medical attention.

An alternative explanation may be that individuals who are prone to shoulder instability have a different genetic makeup of type II collagen. Some studies have evaluated genetic predisposition to both ACL tear and shoulder instability with specific polymorphisms discovered in the COL1A1 gene.\textsuperscript{4,15} Although these changes in type I collagen production may result in the risk of ligament injury, there is little support in the literature for the effect on type II collagen production. However, type II collagen has been isolated in the glenoid labrum, suggesting a possible mechanism for this hypothesis.\textsuperscript{16} This work suggests that differences at the tissue level may help to explain why some patients sustain injury and others do not.

Limitations

Although this study has strengths, it also has limitations. Serum samples were obtained on baseline entry to this prospective study, and injury occurred at different points during the 4-year surveillance period. The authors attempted to match injured subjects with appropriate uninjured control subjects, but errors are possible and may have skewed the results. Finally, the subjects in this study were drawn from a preselected cohort of young, primarily male athletes. This homogeneity may be beneficial for research purposes, but it may limit the ability to extrapolate study data to other populations.

**Conclusion**

This study is the first to describe baseline levels of the cartilage biomarkers collagen type II cleavage and procollagen II carboxy propeptide in patients with shoulder instability. Specifically, significantly lower levels of the cartilage degradation marker collagen type II cleavage were found in subjects with shoulder instability compared with control subjects. This study suggests that differences in baseline cartilage metabolism may play a role in the risk of shoulder instability. An alternative explanation is that subclinical partial shoulder instability may produce a biochemical profile that offers protection against future episodes of instability through mechanisms that have not been identified. Further study is needed to identify the exact mechanism within the shoulder joint that protects against injury.

**References**