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Original Article

Longitudinal measurement of serum cartilage oligomeric matrix protein can detect the progression of cartilage degeneration in anterior cruciate ligament reconstruction patients

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A B S T R A C T

Background/objective: Cartilage oligomeric matrix protein (COMP) has utility as a diagnostic marker for osteoarthritis (OA). Our previous study revealed that the serum COMP level can be used to detect early cartilage change in non-OA patients with anterior cruciate ligament (ACL)-deficiency. However, there are still no studies on detecting the progression of cartilage degeneration in early OA. The aim of present study was to investigate whether serum COMP can detect the progression of cartilage degeneration after ACL reconstruction in non-OA patients.
Methods: Patients without cartilage degeneration of early OA at ACL reconstruction and whose serum COMP levels could be measured were included in the study. Cartilage degeneration of early OA were defined as International Cartilage Repair Society (ICRS) grade 1 to 4 in more than 2 compartments or ICRS grade 2 to 4 in 1 compartment. The patients were divided into two groups: those who had cartilage degeneration of early OA at second-look arthroscopy (cartilage degeneration progression group) and those who did not (non-progression group), and the serum COMP values between the two groups were compared.
Results: Thirty-one patients were included. There were 8 cases (25.8 %) in progression group and 23 cases (74.2 %) in non-progression group. There were significant differences between the two groups regarding age and change in serum COMP level. In terms of the rate of change in COMP, an increase of more than 1.24-fold was the cut-off value for detecting the progression of cartilage degeneration.
Conclusions: In this study, the increase in serum COMP levels was significantly greater in progressed cartilage degeneration group than non-progression group after ACL reconstruction. Longitudinal serum COMP measurement could detect the progression of cartilage degeneration.
Level of evidence: Level III, retrospective comparative study.

1. Introduction

The standards applied for osteoarthritis (OA) diagnosis are usually clinical symptoms and radiographic criteria. However, the disease is initiated long before it can be detected on plain X-rays, and thus when physical or radiographic evidence of OA is established, significant and irreversible disease progression may already have occurred and the optimal time for early treatment is delayed.[1,2] Therefore, with sensitive diagnostic tools prior to radiography, early intervention can be employed that can delay irreversible joint damage. Various treatments for OA such as biological regenerative therapies, chondroplasty, and autologous chondrocyte transplantation have increased the need for early diagnosis of OA before irreversible changes occur.[2–4] To identify a subpopulation of patients who have signs of joint disease and are probably at high risk of developing knee osteoarthritis, recently, criteria for classification of early OA populations have been proposed. However, there are no validated and widely accepted criteria for early knee OA available.

In the diagnosis of OA, magnetic resonance imaging (MRI) is a well-established modality for cartilage assessment in OA. Arthroscopy allows for good visibility and easy palpation of articular cartilage lesions. However, MRI and arthroscopy do have some limitations, such as invasiveness and cost effectiveness. Biomarkers have been used to identify and assess the presence and progression of various diseases. A possible way to detect early OA is to measure metabolites of cartilage repair and degradation in order to reflect changes in joint remodeling.

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One of the metabolites that may be a predictive diagnostic biomarker for OA is Cartilage oligomeric matrix protein Cartilage oligomeric matrix protein (COMP).[5] COMP is a non-collagenous protein related to the thrombospondin family of proteins, and is primarily found in the articular cartilage, tendons, and synovium. COMP has utility as a diagnostic marker for OA.[5] Our previous study investigated the ability of serum COMP to detect early OA (International Cartilage Repair Society (ICRS) grade 1 or 2 cartilage lesions) in patients with anterior cruciate ligament (ACL)-deficient patients. It revealed that the serum COMP level can be used to detect early cartilage change in non-OA patients with ACL-deficiency.[6] However, there are still no studies on detecting the progression of cartilage degeneration in early OA.

Thus, the present study was performed to investigate whether serum COMP can detect the progression of cartilage degeneration after ACL reconstruction in non-OA patients. We hypothesized that longitudinal serum COMP measurement could detect progression of cartilage degeneration after ACL reconstruction.

2. Methods

2.1. Patients

This study was approved by the hospital ethics committee and an internal review board of our institution. Informed consent was obtained from all the enrolled patients. Consecutive patients who underwent ACL reconstruction from February 2012 to April 2018 were retrospectively evaluated. This is the part of our previously reported cohort.[6] We used titanium plate (Double Spike Plate, Smith & Nephew Inc. Endoscopy, Andover, MA, USA) for graft fixation on tibia. When the patient requested removal of the implant, 2nd look arthroscopy was performed. The inclusion criteria were age <50 years, primary ACL injury of Kellgren–Lawrence (KL) grade 0 or 1, without cartilage degeneration of early OA at primary surgery and the availability of serum biomarker levels before ACL reconstruction and 2nd look arthroscopy. Patients with KL grade 2–4 injury, pain or radiographic OA in any other joint, comorbidity with other rheumatic conditions, and previous intra-articular fracture or any other ligament injury in their knee including on the contralateral side were excluded.

2.2. Serum biomarkers

Blood samples (7–8 mL) were collected from patients under fasting conditions after they had rested in a chair for approximately 30 min at the time of each preoperative examination for ACL reconstruction and second look arthroscopy.[7] The samples were allowed to stand for 20 min and then centrifuged at 3000 rpm for 15 min. The serum samples were collected, divided into aliquots, and stored at −80 °C until use. Enzyme-linked immunosorbent assay was used to measure serum COMP levels (#DCMP0; R&D Systems, Minneapolis, MN). The amount of change of serum COMP (ΔCOMP) and the rate of change of serum COMP (change of COMP) were calculated.

2.3. Clinical evaluation

Clinical evaluation was assessed by Lysholm knee score and International Knee Documentation Committee (IKDC) score. Instability was measured using a KT-2000 arthrometer (MED Metric Corp., San Diego, CA) with manual maximum stress and was expressed as the side-to-side difference in millimeters between the injured or reconstructed and normal knees.[8] The Tegner activity scale (TAS) was used to assess activity. All evaluations were performed before the first surgery and 2nd look surgery, respectively.

2.4. Arthroscopic evaluation

All arthroscopic examinations were performed using the medial and lateral parapatellar portals prior to ACL reconstruction surgery by a physician specializing in the knee joint (Y.H.) with 20 years of experience. Intraoperative findings were recorded as to whether or not the meniscus was damaged and what was treated (intact, repair, partial meniscectomy). The evaluation of the cartilage surface on six compartments (the patella, femoral groove, lateral femoral condyle, lateral tibia plateau, medial femoral condyle, and medial tibia plateau) were classified using the International Cartilage Research Society (ICRS) grading system[9] (grade 0: normal cartilage, grade 1: superficial lesions, grade 2: defect less than 50 % of the cartilage depth, grade 3: defect more than 50 % of the cartilage depth, grade 4: defect down to the subchondral bone), and the sites and degrees of cartilage injury were recorded. Cartilage findings in the diagnostic criteria for early OA are defined as including ICRS grade 1–4 in at least two compartments or ICRS grade 2–4 in one compartment.[10] We divided the patients into two groups: those who had cartilage degeneration of early OA at second-look arthroscopy (cartilage degeneration progression group) and those who did not (non-progression group).

2.5. Statistical analysis

A Mann-Whitney *U* test was performed to compare continuous variables (age, body mass index (BMI), preoperative TAS, Lysholm score, IKDC score, KT difference, serum COMP) between progression group and non-progression groups. Fisher exact test was performed for categorical variables (meniscus injury, treatment, and worst ICRS at primary operation). Multivariable logistic regression analysis was performed with adjustment for age and change of COMP to examine the progression of early OA. For the change of serum COMP value, receiver operating characteristic (ROC) analyses were performed to detect the optimum cut-off value, which was calculated by maximizing the sum of sensitivity and specificity in the ROC curve. Differences were considered statistically significant at $p < 0.05$. All analyses were performed with EZR software version 1.38 (Saitama Medical Center, Jichi Medical University, Saitama, Japan).

3. Results

3.1. Subject characteristics

Of the 108 patients with ACL-deficient knees who provided informed consent, 68 patients did not have early OA cartilage findings at the time of ACL reconstruction. Of the 68 patients, 31patients who underwent 2nd look arthroscopy and serum COMP obtained were enrolled in this study. The overall patient characteristics are summarized in Table 1. The mean patient age was 23.2 years (range, 14–49 years), and the mean BMI was 22.2 ± 2.9 kg/m2. Among the 31 patients, 7 were men and 24 were women. The median duration from the time of injury to the time of surgery was 2.7 months (range, 0.9–353 months). The median duration from initial surgery to second look arthroscopy was 12.7 months. The mean Lysholm score improved significantly from 64.4 ± 15.4 preoperatively to 90.2 ± 9.2 at the second look arthroscopy ($P < 0.001$), and the mean IKDC score improved significantly from 59.7 ± 13.3 preoperatively to 78.5 ± 14.6 at the second look arthroscopy ($P < 0.001$). The median serum COMP level was 109.0 (92–136.5) preoperatively and 130.0 (99.5–140.0) at the second look arthroscopy, although there was no statistically significant difference ($P = 0.06$).

3.2. Arthroscopic findings

The cartilage findings at second look arthroscopy using the ICRS grading for each compartment showed in Table .2. There were 154 lesions (82.8 %) unchanged in grade 0, 22 lesions (11.8 %) in grade 1, 8 lesions (4.3 %) in grade 2, and 2 lesions (1.1 %) in grade 3. At second look arthroscopy, there were 8 cases (30.6 %) that met the early OA criteria of arthroscopic cartilage lesions and 23 cases (69.4 %) that did

Table 1
Demographic data and Clinical outcomes in overall patients.

Variables		p value (Comparison with preoperative value)
Age (years)	23.2 ± 10.1	
BMI (kg/m2)	22.2 ± 2.9	
Duration from injury (months, Median IQR)	2.7 (1.85–6.75)	
Preoperative TAS	3.0 ± 0.5	
Preoperative Lysholm score	64.4 ± 15.4	
Preoperative IKDC score	59.7 ± 13.3	
Preoperative KT difference (mm)	6.0 ± 1.8	
Preoperative serum COMP (ng/mL),Median (IQR)	109.0 (92–136.5)	
Intra-operative findings		
Medial meniscus		
intact/injury	15/16	
intact/repair/partial resection	15/11/5	
Lateral meniscus		
intact/injury	25/6	
intact/repair/partial resection	25/4/2	
Cartilage		
worst ICRS (grade 0/1)	23/8	
Duration from 2nd look arthroscopy from primary surgery (month, Median IQR)	12.7 (11.5–19.7)	
TAS at 2nd look arthroscopy	5.3 ± 1.4	<0.001
Lysholm at 2nd look arthroscopy	90.2 ± 9.2	<0.001
IKDC at 2nd look arthroscopy	78.5 ± 14.6	<0.001
KT difference (mm) at 2nd look arthroscopy	0.7 ± 1.4	<0.001
Serum COMP (ng/mL) at 2nd look arthroscopy, Median (IQR)	130.0 (99.5–140.0)	0.061
Δ COMP (ng/mL),Median (IQR)	17.4 (−11.5–33.15)	
Change of COMP,Median (IQR)	1.17 (0.91–1.351)	

Abbreviations: BMI (body mass index), TAS (tegner activity scale), IKDC (International Knee Documentation Committee), KT (KT-2000 arthrometer), COMP (cartilage oligomeric matrix protein), OA (osteoarthritis),IQR(Interquartile Range).

Table 2
The International Cartilage Repair Society (ICRS) articular cartilage injury classification at the time of 2nd look arthroscopy.

ICRS classification	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
PA	28	1	1	1	0
FG	27	1	2	1	0
MFC	22	7	2	0	0
MT	28	3	0	0	0
LFC	29	2	0	0	0
LT	20	8	3	0	0

Abbreviations: ICRS (International Cartilage Research Society), PA (patella), FG (femoral groove), MFC (medial femoral condyle), MT (medial tibia), LFC (lateral femoral condyle), LT (lateral tibia).

not meet the early OA criteria of arthroscopic cartilage lesions.

3.3. Comparison in patients with and without progression of cartilage early OA findings

The patient characteristics according to the presence of early OA criteria of arthroscopic cartilage lesions and the comparison of intraoperative findings between the two groups are summarized in Table 3. There were significant differences between the two groups regarding age. There were no significant differences in other parameters at the time of the first surgery. There was no significant difference between the two groups in terms of intraoperative findings, including the presence of meniscus injury or surgical details. The comparison between the two groups at second look surgery, there were no significant difference except for the changes in serum COMP. The dot chart shows the change of COMP for each of the two groups (Fig. 1).

Table 3
Comparisons in continuous variables between patients with and without progress early OA arthroscopic cartilage lesions.

Variables	Patients with progress early OA (mean ± SD) (n = 8)	Patients without early OA (mean ± SD) (n = 23)	p value
Age (years)	30.5 ± 11.1	20.7 ± 8.6	0.026
BMI (kg/m2)	23.3 ± 2.9	21.8 ± 2.7	0.249
Duration from injury (months, Median,IQR)	2.9 (1.58–4.88)	2.7 (1.95–7.60)	0.513
Preoperative TAS	3.0 ± 0.5	2.9 ± 0.5	0.853
Preoperative Lysholm score	57.8 ± 18.1	66.7 ± 14.1	0.288
Preoperative IKDC score	60.6 ± 14.4	59.4 ± 13.2	0.735
Preoperative KT difference (mm)	5.5 ± 1.4	6.1 ± 2.0	0.597
Preoperative serum COMP (ng/mL),Median (IQR)	96.4 (77.7–111.0)	111.0 (97.4–136.5)	0.203
Intra-operative findings			
Medial meniscus			
intact/injury	2/6	13/10	0.22
intact/repair/resection	2/3/3	13/8/2	0.102
Lateral meniscus			
intact/injury	5/3	20/3	0.161
intact/repair/resection	5/2/1	20/2/1	0.183
Cartilage			
worst ICRS (grade 0/1)	4/4	19/4	0.154
Duration from 2nd look arthroscopy from primary surgery (month, Median IQR)	14.9 (12.6–25.3)	12.5 (11.3–14.7)	0.269
TAS at 2nd look arthroscopy	5.0 ± 1.3	5.3 ± 1.4	0.548
Lysholm at 2nd look arthroscopy	91.6 ± 5.8	89.7 ± 10.1	0.785
IKDC at 2nd look arthroscopy	76.7 ± 14.0	79.1 ± 15.0	0.661
KT difference (mm) at 2nd look arthroscopy	0.6 ± 1.6	0.8 ± 1.4	0.639
COMP (ng/mL) at 2nd look arthroscopy, Median (IQR)	131.0 (120.3–148.0)	126.0 (97.5–135.5)	0.379
Δ COMP (ng/mL),Median (IQR)	38.0 (26.8–42,8)	12.0 (−15.0–22.5)	0.003
Change of COMP,Median (IQR)	1.39 (1.26–1.49)	1.10 (0.89–1.24)	0.026

Abbreviations: BMI (body mass index), TAS (tegner activity scale), IKDC (International Knee Documentation Committee), KT (KT-2000 arthrometer), COMP (cartilage oligomeric matrix protein), OA (osteoarthritis), IQR(Interquartile Range).

Multivariate logistic analyses showed in Table .4. It revealed that age (OR = 1.1, P = 00.034) and change of COMP (OR = 36.7, P = 00.049) significantly increased the risk of early OA progression.

ROC analysis was used to determine the cutoff value of statistically significant variables in diagnosing detecting the progression of cartilage degeneration (Fig. 2). The cutoff value for the increase in serum COMP to detect the progression of cartilage degeneration was 1.24-fold increase. The sensitivity was 87.5 %, and the specificity was 73.9 %. Area under the curves (AUC) were also calculated to estimate the diagnostic accuracy of serum COMP level. The AUC value of change of serum COMP was 0.766.

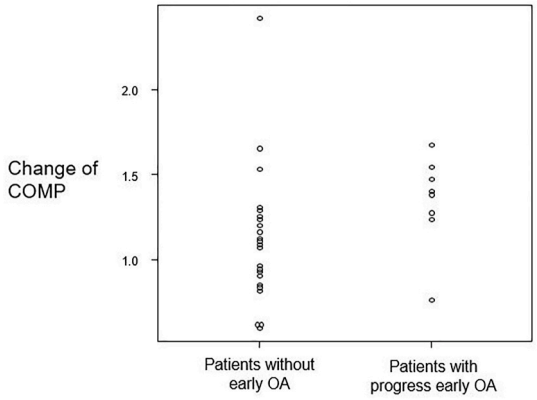

Fig. 1. Dot chart graph was performed for the early OA progression and non-progression groups about the change of COMP.

Table 4
Multivariate analysis of factors associated with early OA progression.

Variables	Odds ratio	95 % CI	p value
Age	1.1	1.01–1.22	0.034
Change of COMP	36.7	1.01–1340.0	0.049

Abbreviations: OA (osteoarthritis), COMP (cartilage oligomeric matrix protein), CI (Confidence interval).

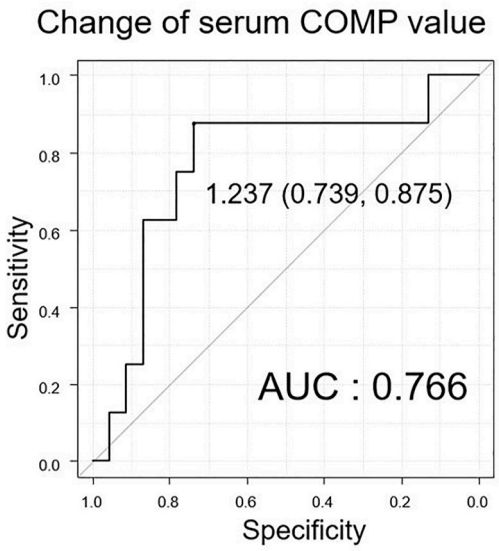

Fig. 2. Receiver operating characteristic curve analysis was used to determine the cutoff value of statistically significant variables in diagnosing detecting the progression of cartilage degeneration. The cutoff value for the increase in serum COMP to detect the progression of cartilage degeneration was 1.24-fold increase. The sensitivity was 87.5 %, and the specificity was 73.9 %. AUCs were also calculated to estimate the diagnostic accuracy of serum COMP level. The AUC value of change of serum COMP was 0.766.

4. Discussion

This study investigated whether serum COMP can detect the progression of cartilage degeneration after ACL reconstruction in non-OA patients. Of the cases in which a second look arthroscopy was performed, the incidence of progression of cartilage degeneration was approximately 30 %, and the increase of serum COMP levels were significantly higher in the progression of cartilage degeneration group than in the non-progression group. The optimal cutoff value for detecting progression to early OA was a 1.24-fold increase in serum COMP change.

Post-traumatic osteoarthritis (PTOA) is a subtype of OA and the incidence of PTOA after ACL injury is reported to be 50–90 %.[11] ACL injuries are responsible for a large number of individuals with early-onset OA and associated pain, functional limitations, and decreased quality of life between the ages of 30 and 50 years.[12,13] Many factors may be involved in the risk of PTOA after an ACL injury, including gender (female), age, high body mass index (BMI), obesity, physical activity level, smoking, low education, subsequent surgery, the time interval between injury and surgery, and varus alignment of the uninjured knee.[14–16] Although the ACL reconstruction helps to control anterior translation of the tibia, restore proper joint kinematics and knee stability, and prevent excessive torsional loading, there is little evidence that it clearly prevents the progression of OA.[17,18] There are several possible reasons why ACL reconstruction surgery may not have a protective effect on long-term joint health. First, surgery cannot fully restore normal joint mechanics.[19] Second, surgery itself could be a trauma to the knee joint.[20] Third, the molecular and cellular changes in the joint tissue caused by ACL injury are not easily reversed by stabilizing the joint.[21] Lee et al. reported PFOA progression in 20 % of patients 3 years after ACL reconstruction, with risk factors including age at surgery and meniscectomy at primary surgery.[22] In this study, there were no cases of obvious instability postoperatively. However, of the 31 patients who had been performed second look arthroscopy after ACL reconstruction, 8 (25.8 %) cases had progressive cartilage damage. There was no difference in the primary surgical procedure for the meniscus, however, age was significantly higher in the group with advanced cartilage degeneration.

There is increasing awareness of the importance in identifying early phases of the degenerative processes during early knee OA. For diagnose of early knee OA,[10] the following criteria are proposed. One is pain in the knee, second is standard radiographs KL grade 0 or I or II (osteophytes only), third is at least one of the two following structural criteria (arthroscopic findings or MRI findings). COMP is an extracellular matrix glycoprotein that is released into circulation when cartilage degenerates and therefore is considered a marker of cartilage breakdown. Serum COMP was reported to be elevated in patients with knee OA[23–25] and increase with severity of OA.[26] It is also elevated in early OA[6] and has been reported to detect cartilage degeneration on arthroscopy.[27] However, limited data are available on whether serum COMP can detect the progression of early knee OA.

Serum COMP levels are elevated after intense exercise.[28,29] Serum COMP levels increased mid and post-season compared to preseason in soccer player.[30] Therefore, elevated levels of serum COMP as a result of physical activity indicates that this biomarker sensitively reflects changes in articular cartilage. Although it is necessary to keep the measurement method constant due to its sensitivity, longitudinal measurement of serum COMP levels, as in this study, could detect the progression of cartilage degeneration at a level comparable to that of arthroscopic findings.

Mendias et al. reported changes in serum COMP over time after ACL reconstruction.[31] They observed a significant decrease in COMP immediately (3 days) after surgery, but otherwise COMP levels were not different from the pre-operative time point. They measured serum COMP levels postoperatively up to 26 weeks and reported that there were no different from the preoperative time point. Our study also showed no significant difference between preoperative and 2nd look time point values, however the values of COMP were slightly higher at the 2nd look point. Since most cases were measured after 1 year postoperatively, it is possible that they detected an increase due to changes over time. This study has lower serum COMP values than their report. This may be due to the slightly lower mean age (23 vs. 28 years) and the exclusion of early OA cases.

This study has several limitations. First, the sample size was small, and second-look arthroscopy was performed in only 31 of the 68

patients. Because of the small sample size, the change of serum COMP value cutoff of 1.25 should be interpreted carefully and deserves further study. Second, the retrospective design of this study presents inherent limitations. Third, the definition of early OA and appropriate outcomes are under development. More recent criteria focus on the patient's symptoms.[32] However, cartilage findings are important for early OA changes, and it is valuable finding that COMP could detect arthroscopic cartilage change. Fourth, factors that contribute to the progression of OA, such as knee alignment, were not investigated. However, the results should not be affected in terms of detecting the progression of cartilage degeneration. Fifth, the day of COMP blood collection and the day of surgery were not the same day, since serum COMP was collected during the outpatient preoperative examination to perform other blood tests. However, no cases differed by more than 2 weeks. Finally, patients with symptoms in other joints are excluded, but it is undeniable that early OA can occur without symptoms.

5. Conclusions

Of the 31 patients who had been performed second look arthroscopy after ACL reconstruction, 8 (25.8 %) cases had progressive cartilage damage. The increase of serum COMP levels were significantly higher in the progression of cartilage degeneration group than in the non-progression group. The optimal cutoff value for detecting progression to early OA was a 1.24-fold increase in serum COMP change. Longitudinal serum COMP measurement could detect the progression of cartilage degeneration.

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Ethical approval

This study was approved by the hospital ethics committee and an internal review board of our institution.

Informed consent

Informed consent was obtained from all the enrolled patients.

Declaration of competing interest

The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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