Original Article

CARTILAGE
July-September 2022: 1–8
© The Author(s) 2022
DOI: 10.1177/19476035221118171
journals.sagepub.com/home/CAR

Biological Effects of High Tibial Osteotomy on Spontaneous Osteonecrosis of the Knee

Ken Kumagai[1], Shunsuke Yamada[1], Shuntaro Nejima[1], Masaichi Sotozawa[1], and Yutaka Inaba[1]

Abstract

Objective. The purpose of this study was to evaluate the postoperative status of spontaneous osteonecrosis of the knee (SONK) after high tibial osteotomy (HTO) with concomitant bone marrow stimulation (BMS) using synovial fluid (SF) biomarkers. *Design*. Twenty patients with SONK who underwent opening wedge HTO were enrolled. Paired SF samples from the affected knee were collected at the time of HTO surgery and at the time of plate removal. SF concentrations of interleukin (IL)-6, IL-8, and matrix metalloproteinase (MMP)-13 were measured by enzyme-linked immunosorbent assays. The Knee Society Score (KSS) and hip-knee-ankle (HKA) angle were assessed before and 2 years after HTO. *Results*. The KSS knee and function scores were significantly improved after HTO (mean changes of 33.8 and 29.4, respectively). The mean HKA angle was changed from mechanical varus (−8.6°) to valgus (5.2°). Concentrations of IL-6, IL-8, and MMP-13 were significantly decreased after HTO (mean changes of −73.7%, −32.4%, and −47.9% from preoperative baseline, respectively). Significant correlations were found between lesion size and concentrations of biomarkers, except for preoperative MMP-13. *Conclusions*. SF levels of biomarkers of inflammation and cartilage degradation were reduced after HTO with a concomitant BMS procedure, suggesting a biological improvement in SONK.

Keywords

spontaneous osteonecrosis of the knee, high tibial osteotomy, synovial fluid, biomarker

Introduction

Spontaneous osteonecrosis of the knee (SONK) is most commonly seen in elderly patients with no risk of secondary osteonecrosis. The lesion is described as a focal subchondral lesion, distinguished from secondary osteonecrosis.[1] Since it progresses rapidly to end-stage osteoarthritis,[2] surgical treatment is often required.

Various surgical treatment options for the management of SONK are available, including joint-preserving procedures and joint arthroplasty.[3-5] It would make sense to select the optimal one on the basis of the pathological condition. Cases with SONK usually show a limited lesion of the superficial subchondral tissue in the medial femoral condyle[6] and varus knee deformity in the advanced stage.[7] In addition, articular cartilage of the lateral tibiofemoral and patellofemoral compartments, the anterior cruciate ligament, and the lateral meniscus are preserved in most cases. Thus, repair of damaged cartilage with a concomitant procedure of valgus correction by high tibial osteotomy (HTO) has been introduced as a joint-preserving procedure.[8]

HTO is a joint-preserving procedure to unload the affected knee compartment, resulting in excellent long-term clinical outcomes for SONK.[9,10] A recent study following cases with SONK for 2 years demonstrated that relatively good cartilage repair was observed in small lesions with a defect size under 4 cm^2 after HTO with a concomitant bone marrow stimulation (BMS) procedure.[8] However, the mechanisms underlying the association between this surgical procedure and the clinical outcomes, and the biological effect of the procedure on the pathological condition of SONK need to be elucidated.

Imaging modalities, such as radiograph or MRI, are conventionally uses to diagnose and assess joint disease severity, but it is difficult to assess biological effects after treatment. On the other hand, synovial fluid (SF) biomarkers allow assessment of the pathological condition of joint tissue.[11,12] Biological effects of HTO for knee osteoarthritis

[1]Department of Orthopaedic Surgery, Graduate School of Medicine, Yokohama City University Hospital, Yokohama, Japan

Corresponding Author:
Ken Kumagai, Department of Orthopaedic Surgery, Graduate School of Medicine, Yokohama City University Hospital, 3-9 Fukuura, Kanazawa-ku, Yokohama 236-0004, Japan.
Email: kumagai@yokohama-cu.ac.jp

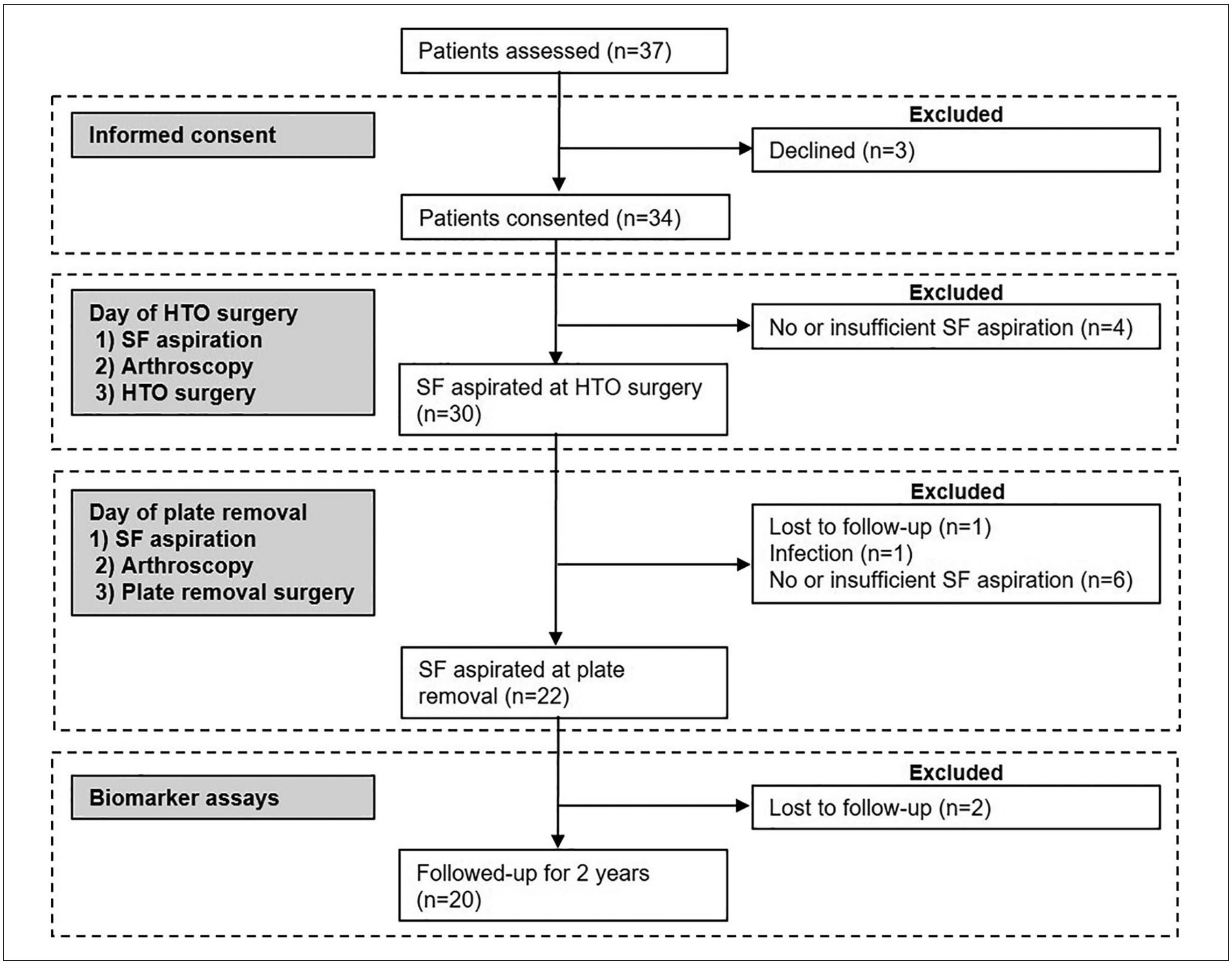

Figure 1. Flow diagram of study subjects. SF = synovial fluid; HTO = high tibial osteotomy.

have recently been demonstrated by investigation of SF biomarkers.[13] In this study, the biological effects of HTO with a concomitant BMS procedure for SONK were investigated using SF biomarkers.

The purpose of this study was to evaluate the postoperative status of SONK after HTO with a concomitant BMS procedure using SF biomarkers. It was hypothesized that (1) SF levels of inflammatory and cartilage degradation biomarkers are changed after HTO with a BMS procedure, and (2) they are associated with lesion size and cartilage repair status.

Materials and Methods

Study Subjects

Patients were included if they satisfied the surgical indications: painful SONK with lesion size <4 cm^2 (calculated by measuring the greatest width and length on MRI) localized to the medial femoral condyle; presence of full-thickness articular cartilage in the lateral and patellofemoral joint compartments confirmed by radiographs of valgus-stress and skyline views and MRI; and no functional instability of the anterior cruciate ligament confirmed by manual tests and MRI. Patients with severe varus deformity with mechanical varus alignment of over 12°, mechanical valgus alignment, flexion contracture greater than 15°, or a history of inflammatory arthritis, joint infection, immunosuppressive therapy, or corticosteroid intake were excluded. A total of 37 knees of 37 consecutive patients with SONK underwent opening wedge HTO and the concomitant BMS procedure between 2015 and 2019, and written, informed consent was obtained from 34 patients for inclusion in this study. All participants agreed with 2-stage aspiration of SF under general anesthesia as the planned research procedures and use of usual clinical care data including radiographs, arthroscopic images, and medical records. Finally, SF biomarkers, cartilage status, and clinical outcomes were investigated in 20 subjects (**Fig. 1**). The study protocol and publication were approved by the Institutional Review Board of Yokohama City University (No: B191100008).

Surgical Procedure and Postoperative Management

An initial arthroscopic examination and BMS were performed prior to HTO on the same day. For BMS, damaged cartilage was removed, and multiple holes approximately 3-4 mm apart with a penetrating subchondral bone plate were created by anterograde drilling with a 2-mm-diameter K-wire in the debrided cartilage defect. HTO was performed using the biplanar opening wedge technique with rigid plate fixation.[10] The amount of angular correction was planned preoperatively, aiming to achieve tibiofemoral mechanical valgus of 5° in a 1-leg standing radiograph postoperatively.

Patients started a postoperative rehabilitation program including isometric quadriceps exercise and range-of-motion exercise the day after surgery. A non-weightbearing regimen was prescribed for 1 week, followed by full weight-bearing exercise. Patients were encouraged to walk with or without a walking aid. Finally, patients achieved step-over-step stair climbing.

Assessment of Clinical and Radiographic Outcomes

All subjects were followed up for 2 years after HTO to assess clinical and radiographic outcomes. Clinical evaluation was carried out using the Knee Society Score (KSS).[14] For radiographic assessment, an anteroposterior, weight-bearing, full-length radiograph of the lower limb was taken, and limb alignment was expressed as the hip-knee-ankle (HKA) angle, which was defined as the angle between the mechanical axes of the femur and tibia, with negative values for varus and positive values for valgus.

Assessment of Articular Cartilage

Second-look arthroscopy was performed in all patients at the time of plate removal, and cartilage repair was evaluated according to the International Cartilage Repair Society (ICRS) repair grade.[15,16]

Biomarker Assays

SF concentrations of interleukin (IL)-6, IL-8, and matrix metalloproteinase (MMP)-13 were measured according to the previously described method.[13] Briefly, paired SF samples were obtained from the affected knee of the same patient just before the arthroscopy at the time of HTO surgery (first aspiration) and at the time of plate removal (second aspiration). The intra-articular fluid was aspirated by a sterile puncture without lavage just prior to the surgery. The samples were immediately centrifuged for 15 minutes at 3,000*g* and 4 °C, and the supernatant was aliquoted and stored at −80 °C until the time of analysis. The SF samples were analyzed with enzyme-linked immunosorbent assays using commercially available test kits (Quantikine, R&D Systems, Minneapolis, MN) according to the manufacturer's instructions.

Table 1. Patients' Demographic Data.

Number of patients	20
Gender, female, *n* (%)	15 (75)
Age, years[a]	69.1 ± 9.3
Body mass index, kg/m[2a]	24.5 ± 5.7
Lesion size, cm^2 (range)	2.8 ± 0.8 (1.4-3.9)
Radiographic classification[9]: stage 1/2/3/4, *n*	0/0/3/17
Postoperative time until second SF aspiration and second-look arthroscopy, mo[a]	15.2 ± 5.1

SF = synovial fluid.
[a]The values are given as mean ± standard deviation.

Statistical Analysis

Statistical analysis was carried out using BellCurve for Excel version 3.21 (Social Survey Research Information Co., Ltd., Tokyo, Japan). Since histograms of the data indicated that the variables had non-normal distributions, non-parametric statistical methods were used to analyze the data. The Wilcoxon signed-rank test was used to test for significant differences in within-subject changes of clinical outcomes and biomarker concentrations. Spearman's rank correlation coefficient was used to identify relationships between SF biomarkers and patients' characteristics or clinical parameters. An adjusted P-value <0.05 was considered significant. The intra-class correlation coefficients for the intra- and inter-rater reliabilities of the measurements were 0.97 and 0.90 for lesion size, 0.87 and 0.85 for HKA angle, and 0.84 and 0.79 for ICRS total score, respectively, suggesting good reliability.

Results

Patients' Characteristics and Descriptive Data

The patients' characteristics are summarized in **Table 1**. The study subjects were 5 male and 15 female patients with a mean age of 69 years. The lesion size was 2.8 (1.4-3.9) cm^2. Second-look arthroscopy was performed 15.2 ± 5.1 months after HTO. Clinical outcomes are summarized in **Table 2**. Knee alignment changed from mechanical varus to valgus in all subjects. The KSS knee and function scores were significantly improved after surgery ($P < 0.05$).

Table 2. Clinical Outcomes.

Variable	Preoperative	Postoperative	*P* Value[a]	Mean Change (95% CI)
HKA angle (°)	−6.2 ± 2.6	4.5 ± 1.9	<0.001	10.7 (9.2, 12.4)
Knee score	58.3 ± 6.7	92.2 ± 5.4	<0.001	33.8 (31.5, 36.2)
Function score	64.5 ± 7.2	93.9 ± 8.1	<0.001	29.4 (25.8, 33.1)

The values are given as mean ± standard deviation.
CI = confidence interval; HKA = hip-knee-ankle.
[a]Wilcoxon signed-rank test.

Table 3. Concentrations of Synovial Fluid Biomarkers.

Biomarker	First Aspiration	Second Aspiration	*P* Value[a]	Mean Change (95% CI)	Percent Change
IL-6, pg/ml	155.5 ± 107.9	29.1 ± 23.2	<0.001	−126.4 (−173.6, −79.2)	−73.7
IL-8, pg/ml	66.3 ± 50.3	29.7 ± 21.6	<0.001	−33.2 (−57.7, −8.7)	−32.4
MMP-13, ng/ml	166.4 ± 128.9	58.6 ± 37.2	<0.001	−107.8 (−164.2, −51.3)	−47.9

First aspiration: at the time of HTO, second aspiration: at the time of plate removal. The values are given as mean ± standard deviation.
CI = confidence interval; IL = interleukin; MMP = matrix metalloproteinase; HTO = high tibial osteotomy.
[a]Wilcoxon signed-rank test.

Table 4. Correlation Analysis between Concentrations of Biomarkers in Synovial Fluid of the First Aspiration and Patients' Characteristics or Clinical Parameters.

	IL-6		IL-8		MMP-1	
	(First Aspiration)[a]		(First Aspiration)[a]		(First Aspiration)[a]	
Variable	r	*P value*	r	*P-value*	r	*P value*
Gender	0.170	0.473	0.175	0.474	−0.130	0.584
Age	−0.085	0.721	0.016	0.948	0.149	0.528
Body mass index	−0.049	0.842	0.269	0.279	−0.126	0.606
HKA angle[b]	−0.017	0.945	−0.119	0.638	0.281	0.244
Knee score[b]	0.012	0.492	−0.092	0.678	0.096	0.724
Function score[b]	0.026	0.917	−0.149	0.554	−0.166	0.497

IL = interleukin; MMP = matrix metalloproteinase; HKA = hip-knee-ankle; r = Spearman's rank correlation coefficient.
[a]At the time of high tibial osteotomy.
[b]Data were obtained before high tibial osteotomy.

SF Biomarkers

Concentrations of SF biomarkers are summarized in **Table 3**. Concentrations of IL-6, IL-8, and MMP-13 were significantly decreased after HTO. Correlation analyses between concentrations of SF biomarkers and patients' characteristics or clinical parameters are summarized in **Tables 4** and **5**.

Relationships between SF Biomarkers and Lesion Size

Concentrations of SF biomarkers were plotted against lesion size (**Fig. 2**). Significant correlations were found between lesion size and concentrations of biomarkers, except for MMP-13 at the time of HTO (first aspiration).

Relationships between SF Biomarkers and Cartilage Repair

Postoperative cartilage status at second-look arthroscopy was grade 2 (nearly normal) in 15 cases and grade 3 (abnormal) in 5 cases according to the ICRS overall repair classification. Concentrations of SF biomarkers were plotted against the ICRS total score (**Fig. 3**). There were no significant correlations between the ICRS total score and concentrations of SF biomarkers.

Discussion

The major advance in this study was the investigation of the biological effects of HTO on SONK. The most important finding of this study was that SF levels of inflammatory and

Table 5. Correlation Analysis between Concentrations of Biomarkers in Synovial Fluid of the Second Aspiration and Patients' Characteristics or Clinical Parameters.

	IL-6 (Second Aspiration)[a]		IL-8 (Second Aspiration)[a]		MMP-13 (Second Aspiration)[a]	
Variable	r	*P Value*	r	*P Value*	r	*P Value*
Gender	0.330	0.155	0.091	0.705	0.361	0.118
Age	−0.285	0.222	−0.149	0.530	−0.080	0.737
Body mass index	0.281	0.244	0.025	0.921	0.128	0.601
Time to second aspiration	0.006	0.980	−0.039	0.872	0.024	0.923
HKA angle[b]	−0.268	0.267	0.063	0.799	−0.081	0.743
Knee score[b]	−0.243	0.317	−0.009	0.970	−0.019	0.939
Function score[b]	−0.085	0.728	−0.098	0.690	−0.110	0.653

IL = interleukin; MMP = matrix metalloproteinase; HKA = hip-knee-ankle; r = Spearman's rank correlation coefficient.
[a]At the time of plate removal.
[b]Data were obtained at 2 years after high tibial osteotomy.

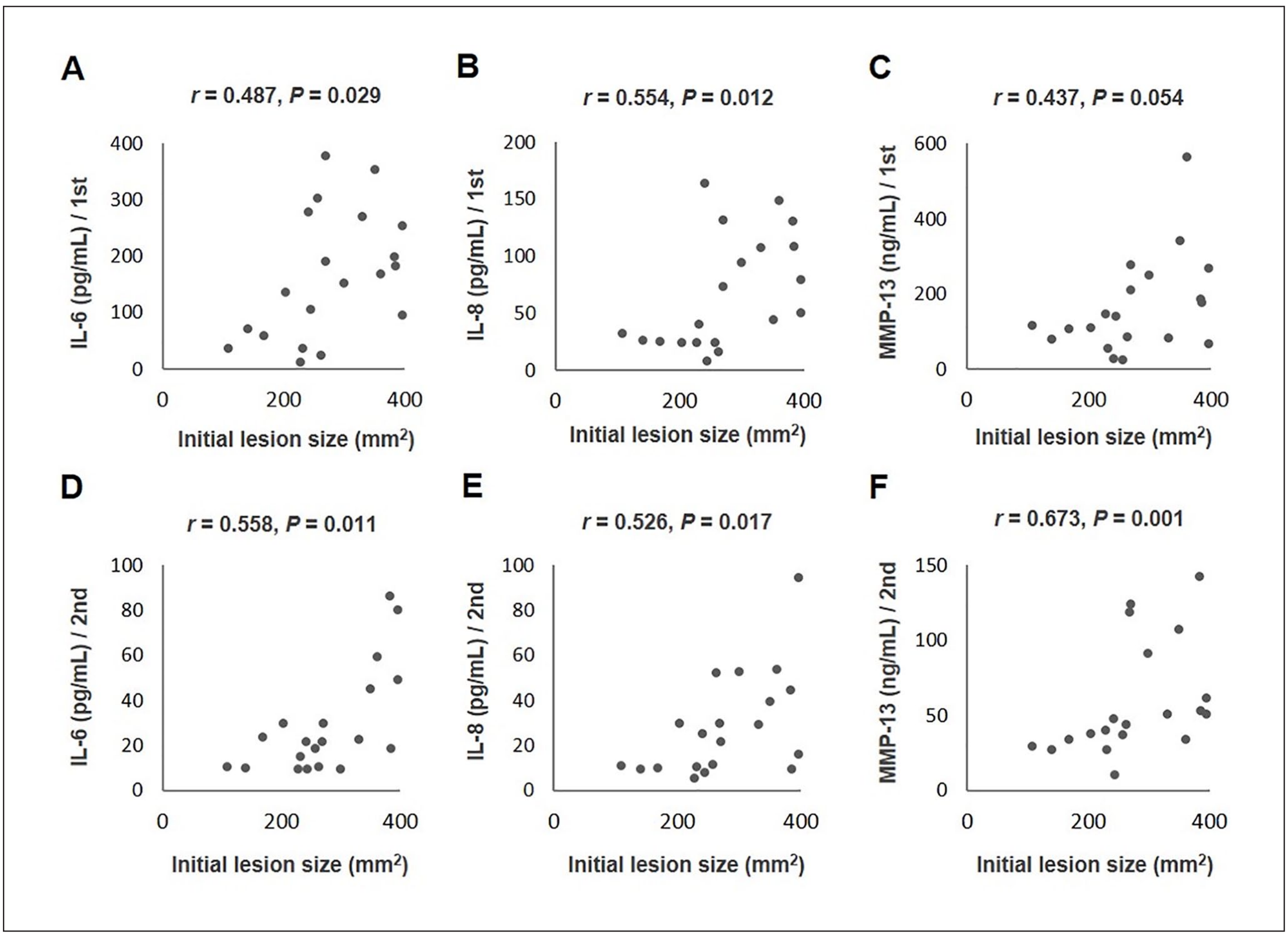

Figure 2. Dot plot graphs for relationships between initial lesion size and synovial fluid biomarkers at the time of high tibial osteotomy (first aspiration, **A**-**C**) and at the time of plate removal (second aspiration, **D**-**F**). Correlations determined using Spearman's rank correlation coefficient. (**A**) IL-6, r = 0.487, *P* = 0.029. (**B**) IL-8, r = 0.554, *P* = 0.012. (**C**) MMP-13, r = 0.437, *P* = 0.054. (**D**) IL-6, r = 0.558, *P* = 0.011. (**E**) IL-8, r = 0.526, *P* = 0.017. (**F**) MMP-13, r = 0.673, *P* = 0.001. MMP = matrix metalloproteinase; IL = interleukin.

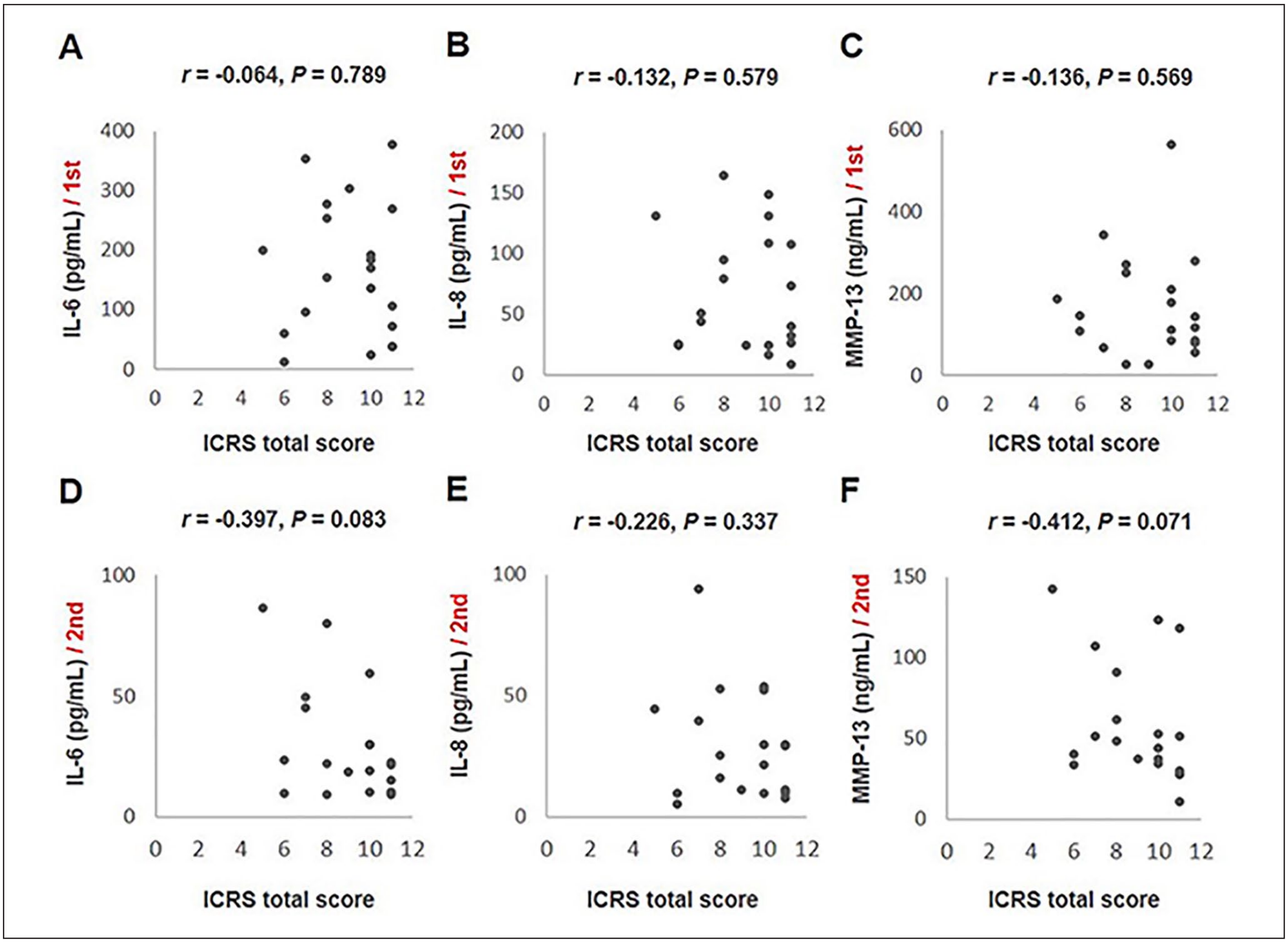

Figure 3. Dot plot graphs for relationships between the ICRS total score and synovial fluid biomarkers at the time of high tibial osteotomy (first aspiration, **A**-**C**) and at the time of plate removal (second aspiration, **D**-**F**). (**A**) IL-6, $r = -0.064$, $P = 0.789$. (**B**) IL-8, $r = -0.132$, $P = 0.579$. (**C**) MMP-13, $r = -0.136$, $P = 0.569$. (**D**) IL-6, $r = -0.397$, $P = 0.083$. (**E**) IL-8, $r = -0.226$, $P = 0.337$. (**F**) MMP-13, $r = -0.412$, $P = 0.071$. ICRS = International Cartilage Repair Society; MMP = matrix metalloproteinase; IL = interleukin.

cartilage degradation biomarkers in SONK were reduced after HTO with a concomitant BMS procedure. The present study also demonstrated that concentrations of those biomarkers in SF were associated with lesion size, but not with cartilage repair status.

Several molecules related to joint metabolism and inflammation are present in the body fluids and can be used for biological monitoring of pathological conditions in joint diseases. Numerous efforts have been undertaken to use the biomarkers for osteoarthritis. The disease state of osteonecrosis includes cartilage damage and synovial inflammation, and the biomarkers reflecting these pathological conditions are likely similar to those for osteoarthritis.[17-20] The present study focused on the changes of SF biomarkers in response to biological improvement of the intra-articular condition. Use of biomarkers as a tool for evaluation of treatment effects on the disease state of SONK is a current challenge.

HTO with a concomitant BMS procedure is a joint-preserving treatment option for SONK with a small lesion.[8] Marrow-stimulating procedures such as drilling and microfracture enable bone marrow containing mesenchymal stem cells to enter the cartilage defect and promote fibrocartilage healing.[21,22] Clinical outcomes were significantly improved after arthroscopic microfracture treatment in patients with SONK.[23] However, patients with a lesion larger than 4 cm^2 had worse clinical outcomes and cartilage repair than did those with a smaller defect.[8,24] Therefore, the surgical indication for BMS was limited to lesion size <4 cm^2. In addition, good clinical outcomes are also associated with improvement of the mechanical environment after HTO. The presence of varus deformity inhibits the healing potential of necrotic lesions[7,25] and is a potential failure risk with an isolated procedure of cartilage repair.[26,27]

Effects of surgical treatment are usually evaluated by improvement of symptoms and function without examination of biological status. This study demonstrated the effects of HTO with concomitant BMS on SONK as reflected by changes of SF biomarkers, as well as clinical outcomes and cartilage repair. Reduced levels of SF biomarkers including IL-6, IL-8, and MMP-13 were also seen after HTO in patients with knee osteoarthritis.[13] The results suggested similar biological effects of HTO on disease status in both knee osteoarthritis and SONK. Most cases with SONK who undergo surgical treatment tend to be categorized as advanced stage, and a similar pattern of biological markers may be suggested in both knee osteoarthritis and SONK.

Markers related to cartilage degradation and synovial inflammation may be accurate indicators of the progression and severity of SONK. A previous study analyzing SF demonstrated that levels of biomarkers, including of cartilage metabolism, were associated with progression of the radiographic stage and size of the necrotic lesion in SONK,[20] and levels of inflammatory cytokines were higher in advanced osteonecrosis of the femoral head.[17] The present study demonstrated that levels of SF biomarkers were correlated with lesion size, although there were no relationships between SF biomarkers and cartilage repair status. These results suggested that the extent of lesion size affects the pathological condition and the improvement of the disease state.

This study has several limitations. First, the investigation analyzing SF was limited to only 3 biomarkers. Second, the study subjects were limited by the ability to collect paired SF samples at the time of HTO and at the time of plate removal. Third, postoperative investigation was performed only once. The findings were limited by the follow-up duration, which was only until the time of plate removal, and mid- to long-term results are unknown. Fourth, the sample size was too small for multivariate analysis. Thus, findings related to factors affecting SF biomarkers are restricted.

Conclusions

SF levels of biomarkers for inflammation and cartilage degradation were decreased after HTO with a concomitant BMS procedure in patients with SONK. These results provide insight into the biological effects of HTO on SONK.

Acknowledgments and Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

The study was approved by the Institutional Review Board of Yokohama City University.

ORCID iD

Ken Kumagai https://orcid.org/0000-0002-7529-0343

References

1. Ahuja SC, Bullough PG. Osteonecrosis of the knee. A clinicopathological study in twenty-eight patients. J Bone Joint Surg Am. 1978;60(2):191-7.
2. Jureus J, Lindstrand A, Geijer M, Robertsson O, Tagil M. The natural course of spontaneous osteonecrosis of the knee (SPONK): a 1- to 27-year follow-up of 40 patients. Acta Orthop. 2013;84(4):410-4.
3. Karim AR, Cherian JJ, Jauregui JJ, Pierce T, Mont MA. Osteonecrosis of the knee: review. Ann Transl Med. 2015;3:6.
4. Lieberman JR, Varthi AG, Polkowski GG 2nd. Osteonecrosis of the knee—which joint preservation procedures work? J Arthroplasty. 2014;29(1):52-6.
5. Mont MA, Marker DR, Zywiel MG, Carrino JA. Osteonecrosis of the knee and related conditions. J Am Acad Orthop Surg. 2011;19(8):482-94.
6. Yamamoto T, Bullough PG. Spontaneous osteonecrosis of the knee: the result of subchondral insufficiency fracture. J Bone Joint Surg Am. 2000;82(6):858-66.
7. Nakayama H, Iseki T, Kanto R, Daimon T, Kashiwa K, Yoshiya S. Analysis of risk factors for poor prognosis in conservatively managed early-stage spontaneous osteonecrosis of the knee. Knee. 2016;23(1):25-8.
8. Kumagai K, Akamatsu Y, Kobayashi H, Kusayama Y, Saito T. Mosaic osteochondral autograft transplantation versus bone marrow stimulation technique as a concomitant procedure with opening-wedge high tibial osteotomy for spontaneous osteonecrosis of the medial femoral condyle. Arthroscopy. 2018;34(1):233-40.
9. Koshino T. The treatment of spontaneous osteonecrosis of the knee by high tibial osteotomy with and without bone-grafting or drilling of the lesion. J Bone Joint Surg Am. 1982;64:47-58.
10. Saito T, Kumagai K, Akamatsu Y, Kobayashi H, Kusayama Y. Five- to ten-year outcome following medial opening-wedge high tibial osteotomy with rigid plate fixation in combination with an artificial bone substitute. Bone Joint J. 2014;96-B(3):339-44.
11. Henrotin Y. Osteoarthritis in year 2021: biochemical markers. Osteoarthritis Cartilage. 2022;30(2):237-48.
12. Nguyen LT, Sharma AR, Chakraborty C, Saibaba B, Ahn ME, Lee SS. Review of prospects of biological fluid biomarkers in osteoarthritis. Int J Mol Sci. 2017;18:601.
13. Kumagai K, Fujimaki H, Yamada S, Nejima S, Matsubara J, Inaba Y. Changes of synovial fluid biomarker levels after opening wedge high tibial osteotomy in patients with knee osteoarthritis. Osteoarthritis Cartilage. 2021;29(7):1020-8.
14. Insall JN, Dorr LD, Scott RD, Scott WN. Rationale of the knee society clinical rating system. Clin Orthop Relat Res. 1989(248):13-4.
15. Brittberg M, Winalski CS. Evaluation of cartilage injuries and repair. J Bone Joint Surg Am. 2003;85-A(Suppl 2):58-69.
16. Brittberg M, Peterson L. Introduction to an articular cartilage classification. ICRS Newsletter. 1998;1:5-8.
17. Abe H, Sakai T, Ando W, Takao M, Nishii T, Nakamura N, *et al*. Synovial joint fluid cytokine levels in hip disease. Rheumatology. 2014;53(1):165-72.

18. Floerkemeier T, Budde S, Willbold E, Schwarze M, Niehof M, Lichtinghagen R, *et al*. Do biomarkers allow a differentiation between osteonecrosis of the femoral head and osteoarthritis of the hip? A biochemical, histological and gene expression analysis. Osteoarthritis Cartilage. 2021;29(11):1614-23.
19. Grassel S, Beckmann J, Rath B, Vogel M, Grifka J, Tingart M. Expression profile of matrix metalloproteinase-2 and -9 and their endogenous tissue inhibitors in osteonecrotic femoral heads. Int J Mol Med. 2010;26(1):127-33.
20. Saito T, Takeuchi R, Mitsuhashi S, Uesugi M, Yoshida T, Koshino T. Use of joint fluid analysis for determining cartilage damage in osteonecrosis of the knee. Arthritis Rheum. 2002;46(7):1813-9.
21. Frisbie DD, Oxford JT, Southwood L, Trotter GW, Rodkey WG, Steadman JR, *et al*. Early events in cartilage repair after subchondral bone microfracture. Clin Orthop Relat Res. 2003;407:215-27.
22. Pridie K. A method of resurfacing osteoarthritic knee joints. J Bone Joint Surg Br. 1959;41:6l8-9.
23. Akgun I, Kesmezacar H, Ogut T, Kebudi A, Kanberoglu K. Arthroscopic microfracture treatment for osteonecrosis of the knee. Arthroscopy. 2005;21(7):834-43.
24. Knutsen G, Engebretsen L, Ludvigsen TC, Drogset JO, Grontvedt T, Solheim E, *et al*. Autologous chondrocyte implantation compared with microfracture in the knee. A randomized trial. J Bone Joint Surg Am. 2004;86-A:455-64.
25. Motohashi M, Morii T, Koshino T. Clinical course and roentgenographic changes of osteonecrosis in the femoral condyle under conservative treatment. Clin Orthop Relat Res. 1991;266:156-61.
26. Bode G, Schmal H, Pestka JM, Ogon P, Sudkamp NP, Niemeyer P. A non-randomized controlled clinical trial on autologous chondrocyte implantation (ACI) in cartilage defects of the medial femoral condyle with or without high tibial osteotomy in patients with varus deformity of less than 5 degrees. Arch Orthop Trauma Surg. 2013;133:43-9.
27. Ghazavi MT, Pritzker KP, Davis AM, Gross AE. Fresh osteochondral allografts for post-traumatic osteochondral defects of the knee. J Bone Joint Surg Br. 1997;79:1008-13.