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

Ken Kumagai1, Shunsuke Yamada1, Shuntaro Nejima1, Masaichi Sotozawa1, and Yutaka Inaba1

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 condyle6 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 cm2 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 used 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...
have recently been demonstrated by investigation of SF biomarkers. 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 cm² (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. 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). 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.

**Biomarker Assays**

SF concentrations of interleukin (IL)-6, IL-8, and matrix metalloproteinase (MMP)-13 were measured according to the previously described method. 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 3,000g 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.

**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) cm². 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).
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 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 cartilage repair biomarkers were significantly decreased after HTO.

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

| Variable                      | IL-6 (Second Aspiration) | IL-8 (Second Aspiration) | MMP-13 (Second Aspiration) |
|-------------------------------|---------------------------|--------------------------|-----------------------------|
|                               | 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<sup>b</sup>         | −0.268       | 0.267       | 0.063        | 0.799       | −0.081       | 0.743       |
| Knee score<sup>b</sup>        | −0.243       | 0.317       | −0.009       | 0.970       | −0.019       | 0.939       |
| Function score<sup>b</sup>    | −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.

<sup>a</sup>At the time of plate removal.

<sup>b</sup>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.
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 cm² 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 cm². 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 lesions7,25 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.\textsuperscript{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,\textsuperscript{20} and levels of inflammatory cytokines were higher in advanced osteonecrosis of the femoral head.\textsuperscript{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.

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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.

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ORCID iD

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