Under-Correction Associated with Residual Proinflammatory Cytokine Gene Expressions After High Tibial Osteotomy

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INTRODUCTION:

Medial open wedge high tibial osteotomy (MOWHTO), which realigns the lower limb alignment from varus to valgus, is widely performed for medial knee osteoarthritis (OA). While biomechanical studies have demonstrated that MOWHTO decreases medial compartment loading, it remains unclear whether optimizing knee alignment affects joint inflammation in the biological microenvironment. Previous research has reported a reduction in the expression of pro-inflammatory cytokines and chemokines, as well as a shift in synovial macrophage polarity from M1 to M2 in synovial tissues (STs) after MOWHTO. However, the relationship between alignment correction and synovial gene expression has not been fully elucidated. Therefore, the purpose of this study was to evaluate the relationship between pre- and postoperative knee alignment and synovial gene expression, and to determine the cutoff point of postoperative knee alignment at which synovial inflammation gene expressions improve.

METHODS:

This investigation was approved by the institutional review board, and all patients provided written informed consent to participate. This study included consecutive patients with medial compartment OA of the knee who underwent MOWHTO between 2018 and 2020. All patients were followed-up postoperatively until the time of plate removal approximately one year to assess of clinical and radiographic outcomes. Clinical evaluation was carried out using knee injury and osteoarthritis outcome scores (KOOS) preoperatively and postoperatively (at the time of plate removal). For radiographic assessment, the weight bearing line ratio (WBLR) (<50% indicates varus alignment) and the hip-knee-ankle angle (HKAA) (positive value indicates varus alignment) were measured with anteroposterior whole-leg standing radiography. An initial arthroscopic examination was routinely performed prior to MOWHTO. Synovial tissues (STs) were harvested from the suprapatellar pouch during arthroscopic examination. MOWHTO was performed with target WBLR of 60-62.5%. Then the osteotomy was fixed with a locking plate. Plate removal was performed about one year after OWHTO when bone healing was confirmed, and STs were collected from suprapatellar pouch during arthroscopic examination prior to plate removal.

Total RNA was extracted and purified from fresh STs samples followed by reverse transcription. Then, real-time PCR was performed in triplicate for each sample to determine relative gene expression using glyceraldehyde 3-phosphate dehydrogenase (GAPDH) as a housekeeping control using the $2^{-\Delta\Delta Ct}$ method.

Corelations between lower limb alignments and synovial gene expressions were determined using Spearman rank correlations. A receiver operating characteristic curve (ROC) analysis was used to determine the cut-off values of WBLR for improvement of gene expression from preoperative to postoperative. $P < 0.05$ was considered as significant.

RESULTS:

A total of 40 patients were enrolled, and four patients without plate removal were excluded. The mean age of analyzed 36 patients was 61.4 ± 7.1 years, and sex was female dominant (male 16, female 20). Mean preoperative HKAA was 8.3 ± 4.2° varus, which was corrected to 0.6 ± 2.6° valgus, postoperatively. Pre- and postoperative WBLR was 14.6 ± 16.2% and 51.4 ± 9.4 %, respectively. Plates were removed 13.9 ± 3.7 months after OWHTO. Postoperative HKAA was correlated with *IL1B* ($\rho = 0.47$, $p = 0.004$) and *IL6* ($\rho = 0.42$, $p = 0.01$), and postoperative WBLR also correlated with *IL1B* ($\rho = -0.43$, $p = 0.008$) and *IL6* ($\rho = -0.41$, $p = 0.01$), indicating knees with postoperative under-correction associated with high expression of proinflammatory cytokines. In ROC analysis, ROC curves for postoperative WBLR to postoperative improvement of gene expression of *IL1B* and *IL6* were drawn (Fig 1) with AUCs of 0.62 ($p = 0.27$) and 0.74 ($p = 0.03$), respectively. The cutoff value to predict improvement of *IL6* was postoperative WBLR = 52%. There were significant differences in postoperative proinflammatory cytokine gene expressions between the patients with WBLR <52% and >52% (Fig 2). Patients with WBLR <52% showed inferior postoperative every KOOS scale to those with WBLR >52%. When pre-operative WBLR >0% (n = 30), postoperative WBLR was <52% in 11 cases and >52% in 19 cases. However, when preoperative WBLR <0% (n =6), no patients achieved postoperative WBLR >52% ($p = 0.006$) (Fig. 3).

DISCUSSION AND CONCLUSION:

From this study, relationship between knee alignment and gene expressions were observed after MOWHTO, and patients with under-correction tended to have insufficient improvement of proinflammatory cytokine expressions. The postoperative alignment to predict improvement of *IL6* gene expression was WBLR = 52%, which was considered as the minimum postoperative alignment for biological improvement.

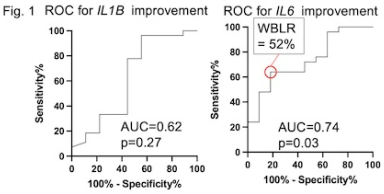
Fig. 1 ROC for IL1B improvement
ROC for IL6 improvement
Sensitivity%
100% - Specificity%
AUC=0.62
p=0.27
WBLR
= 52%
AUC=0.74
p=0.03

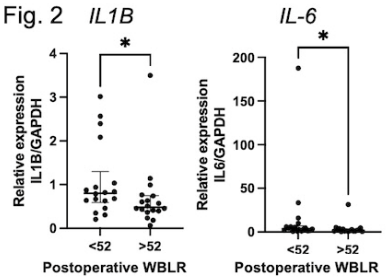
Fig. 2 IL1B
IL-6
Relative expression
IL1B/GAPDH
IL6/GAPDH
<52
>52
Postoperative WBLR

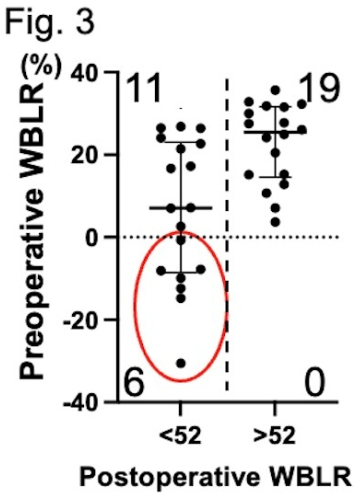
Fig. 3
Preoperative WBLR (%)
11
19
6
0
<52
>52
Postoperative WBLR