THE CONCENTRATION OF EXTRACELLULAR MATRIX METALLOPROTEINASE INDUCER (EMMPRIN) IN EXUDATES IN THE KNEE JOINT AFTER TOTAL KNEE ARTHROPLASTY IS CORRELATED WITH THE POSTOPERATIVE RANGE OF KNEE MOTION

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INTRODUCTION:
Total knee arthroplasty (TKA) can provide pain relief and improvement in gait ability to patients who suffer from serious joint destruction. However, some patients frequently fail to gain sufficient range of knee motion (ROM) postoperatively. Previous studies have reported that various intra- and post-operative factors, including preoperative ROM, prosthesis design, ligament balance, and post-operative rehabilitation, cause the postoperative reduction of ROM [1]. No investigators, however, have studied whether any biological factors cause the postoperative reduction of ROM after TKA. To study on this tissue, the authors have focused on the exudates from the injured bone and connective tissues after TKA. There is a strong possibility that the exudates contain various soluble factors that affect anabolic or catabolic connective tissues after TKA. There is a strong possibility that the exudates contain various soluble factors that affect anabolic or catabolic mechanism of collagen and proteoglycans, such as extracellular matrix metallo-proteinase inducer (EMMPRIN), matrix metalloproteinase (MMP), tissue inhibitor of matrix metalloproteinases (TIMP), and so on, because, clinically, fibrosis or fibrous adhesion in the joint are frequently observed in the knees with narrow ROM reduced after TKA. We hypothesized that there are some soluble factors correlated with the postoperative ROM in the exudates from the bone and connective tissues after TKA. The purpose of this study is to test this hypothesis.

METHODS:
This prospective study was carried out under the Role and Regulation of the Human Research Committee, Hokkaido University, and informed consent was obtained from all patients. Twenty patients (3 men and 17 women) with osteoarthritic knees underwent TKA in the unilateral knee. The mean patient age at the time of surgery was 71.3 years (range, 58-83 years). The preoperative ROM averaged 127 degrees (range, 90-145 degrees). TKA was performed using the same cruciate-retention-type prosthesis by one experienced surgeon. In all the patients, ligament balancing was successfully achieved with the standard TKA technique so that almost full ROM was obtained during surgery. After surgery, each patient was allowed unrestricted activity on the bed without any immobilization, but weight-bearing and rigorous knee motion exercise was restricted for 48 hours. Joint fluid samples were obtained from a continuous drainage system at 48 hour using a sterilized technique. The collected joint fluid was centrifuged at 3,000 rpm, and the aliquots of supernatants were stored at -80°C until analytical use. We measured the concentration of EMMPRIN, MMP-1, 2, 9, and TIMP-1 with enzyme-linked immunosorbent assay (ELISA). Hereafter, the standard postoperative rehabilitation was performed using the same protocol, and active knee motion exercise was encouraged. We measured the maximum flexion angle using a radiogram in a lateral view at 4 weeks after surgery. Statistical analyses were made using the Person’s regression analysis. The significance level was set at p<0.05.

RESULTS:
There was significant positive correlation (p=0.016) between the concentration of EMMPRIN and the ROM measured at 4 weeks (Fig. 1). Significant positive correlation (p=0.012) was also found between the concentration of TIMP-1 and the ROM at 4 weeks (Fig. 2). There was no significant correlation between the concentration of each MMP and the ROM (Table 1). Additionally, there was no significant correlation between each concentration value and the preoperative ROM.

DISCUSSION:
This study demonstrated that the concentration of EMMPRIN and TIMP-1 in exudates after TKA is significantly correlated with the postoperative ROM. EMMPRIN is a glycoprotein with a molecular weight of approximately 58,000 that belongs to immunoglobulin superfamily. EMMPRIN is considered to play important roles in pathological or physiological conditions such as tumor cell invasion, metastasis, arthritis, and tissue repair process by inducing production of functional molecules including MMPs. Although EMMPRIN can stimulate fibroblasts to synthesize MMP-1, -2, -3, -9, -14, and -15 [2], there were no correlations between the concentration of EMMPRIN and each MMP value. In addition, although MMPs are considered as molecules having catabolic actions in collagen metabolism, we could not detect any significant correlation between the concentration of each MMP and the postoperative ROM. Therefore, this study implied that EMMPRIN may affect the postoperative collagen metabolism in the knee joint after TKA through a mechanism independent of MMPs, because a recent study reported that EMMPRIN induces various functional molecules [3]. On the other hand, the concentration of TIMP-1, a common inhibitor for MMPs, was positively correlated with the ROM. However, a mechanism of the effect of TIMP-1 was not clarified in the present study. Further studies should be conducted to clarify the mechanisms of the correlation between the postoperative ROM and EMMPRIN was well as TIMP-1 in the near future. As to clinical relevance, it is clinically important to make effort to find out an indicator to predict postoperative ROM in patients with TKA immediately after surgery. This study suggested that EMMPRIN is a promising indicator to predict it.

REFERENCE:

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Table 1. Relationship between each soluble factor in the exudates at 48 hours after TKA and the postoperative ROM measured.

<table>
<thead>
<tr>
<th>Soluble factor</th>
<th>Coefficient of correlation (p value)</th>
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<tbody>
<tr>
<td>EMMPRIN</td>
<td>r=0.557 (p=0.016)</td>
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<tr>
<td>TIMP-1</td>
<td>r=0.562 (p=0.012)</td>
</tr>
<tr>
<td>MMP-1</td>
<td>r=0.236 (p=0.759)</td>
</tr>
<tr>
<td>MMP-2</td>
<td>r=0.171 (p=0.471)</td>
</tr>
<tr>
<td>MMP-9</td>
<td>r=-0.337 (p=0.147)</td>
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52nd Annual Meeting of the Orthopaedic Research Society
Paper No: 0401