INTRODUCTION:
Local administration of therapeutic agents to joints is reasonable in the treatment of osteoarthritis (OA). However, maintenance of effective concentration of proteins is difficult because usual proteins are metabolized immediately when direct administration into joints is performed. Therefore, it is important for the cartilage treatment using biological factors to control effective local concentrations. We reported that sustained release of basic fibroblast growth factor (bFGF) in joints using the gelatin microspheres had a therapeutic effect in a rabbit model (1). In this study, the kinetics of bFGF release in joint and the mechanism of this therapeutic effect were investigated.

METHODS:
$^{125}$I labeled bFGF contained in gelatin microspheres was administered into the knee joints of normal rabbits to confirm the sustained release kinetics. In addition, the expressions of proteoglycan core protein mRNA in the cartilage was analysed using real-time PCR.

Fifty seven male Japanese white rabbits (2kg) underwent transection of the anterior cruciate ligament (ACLT) of the left knee and were divided into six groups. Control Group: no injection after ACLT ($n=15$); PBS-M Group: injections of PBS contained in gelatin microspheres ($n=7$); 10-bFGF-S and 100-bFGF-S Groups: injections of 10 µg ($n=6$) and 100 µg ($n=5$) bFGF solutions, respectively; 10-bFGF-M and 100-bFGF-M Groups: injections of 10 µg ($n=11$) and 100 µg ($n=13$) bFGF contained in gelatin microspheres, respectively. All injections were performed 4 and 7 weeks after ACLT. All ACLT knees were evaluated for gross morphological changes of cartilage and classified into 6 grades [Grade 1 (intact articular surface), 2, 3, 4a, 4b and 4c (severely degenerated articular surface)] and scored from 0 to 5 at 10 weeks after the transection. Synovium and cartilage were examined histologically.

RESULTS:
bFGF remained in the joint decreased to approximately 11.7% and 3.4%, 3 and 7 days after administration of bFGF-M, respectively, while the expression of proteoglycan core protein mRNA in the articular cartilage increased for 14 days after administration (Figure 1).

Severely damaged cartilage (over Grade 4a) was observed in 60% of Control Group, 43% of PBS-M Group, 50% of 10-bFGF-S Group, 40% of 100-bFGF-S Group, 18% of 10-bFGF-M Group, and 15% of 100-bFGF-M Group. Averaged scores were 2.8, 2.3, 2.7, 2.6, 1.2 and 0.7 respectively. The extent and grade of cartilage damage in 10-bFGF-M and 100-bFGF-M Groups were significantly less severe than Control Group (Figure 2). The score of 10-bFGF-M and 100-bFGF-M Groups was also significantly lower than Control Group at the Mankin’s histochemical grading (Figure 3).

DISCUSSION:
bFGF stimulates matrix synthesis and cell growth in chondrocyte (2) and is thought to be an important factor for cartilage repair (3). Recently gelatin hydrogel was reported to achieve controlled release of growth factors in the condition that maintained the biological activity of growth factors (4). The present study demonstrated injection of bFGF contained in gelatin microspheres into joint stimulated the cartilage metabolism and induced a therapeutic effect on OA development in a rabbit model. Our results suggest the potential feasibility of a new conservative treatment for OA.

REFERENCES:
(1) Inoue A, et al. 51th annual meeting of the ORS 2005