Spontaneous Recurrent Hemarthrosis of the Knee in the Elderly: Arthroscopic Treatment and Etiology

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Purpose: To elucidate the etiology of and find a preferable surgical treatment for spontaneous recurrent hemarthrosis in osteoarthritic knee joints arthroscopically. **Methods:** Nineteen patients referred to our institution from affiliate hospitals between April 1998 and October 2006 were involved in this study. Their demographics, preoperative radiographic findings, preoperative magnetic resonance imaging (MRI) findings, arthroscopic findings and procedures performed, the patient's medical history, and the postoperative clinical course were retrospectively reviewed. **Results:** There were 9 male and 10 female patients with average age of 61.9 years (range, 41 to 83 yrs). The average number of joint aspirations before surgery was 5.4. The average time from onset to arthroscopy was 10 months. Radiographs showed 2 knees with isolated lateral compartment osteoarthritis (OA), one with isolated patellofemoral (PF) OA, 14 with medial and lateral compartment OA, and 2 with tricompartmental OA. Classifying them according to the dominant compartment, 6 knees were medial-dominant OA, 11 lateral-dominant OA, and 2 PF-dominant OA. The MRI scans revealed 18 grade III lateral menisci and 1 grade II lateral menisci. Even with 6 medial-dominant OAs, lateral meniscal involvement was more obvious than medial meniscal involvement on MRI. Subtotal lateral meniscectomy accompanied with coagulation of the bleeding points was performed on 17 cases. For 2 PF OA cases, synovectomy and a histologic examination of synovium were performed. Remission was obtained for 18 cases. The unsuccessful case had cirrhosis of the liver. **Conclusions:** A majority of the patients (17 of 19) had degenerative torn lateral menisci confirmed with MRI and at arthroscopy. Successful outcomes were achieved by meniscectomy and coagulation. Most so-called spontaneous recurrent hemarthroses in OA knee joints appear to be attributable to torn lateral menisci. **Level of Evidence:** Level IV, therapeutic case series. **Key Words:** Arthroscopy—Elderly—Knee—Lateral meniscus—Osteoarthritis—Spontaneous recurrent hemarthrosis.

In 1959, Wilson[1] reported 5 cases of spontaneous recurrent hemarthrosis in the elderly as spontaneous hemarthrosis in knee joints with osteoarthritis (OA). He described the common features of hemarthrosis as being of rapid onset and having tense effusion without any initiating injury.[1] In his report, patellofemoral (PF) joint OA was implicated as the cause of this condition. Since then, several reports have described this disease, including mostly successful treatment outcomes.[2-5] As for surgical treatment, in 1964 Burman et al.[2] reported that synovectomy accompanied with medial and lateral meniscectomy was successful. Morii et al.[3] also reported successful surgical outcomes for 16 patients, and stressed the importance of synovectomy through unicompartmental

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knee arthroplasty for 2 cases, lateral meniscectomy for 4 cases, transfer of tibial tuberosity for 2 cases, and the resection of osteopytes for 5 cases; these were performed as accompanying procedures. In 1994, Kawamura et al.[4] first reported a specific pathology of the knee joint as the cause of hemarthrosis (i.e., degeneratively torn lateral meniscus). They reported that lateral meniscectomy alone gave successful results for 5 surgically treated cases. Pellacci et al.[5] and Ogawa et al.[6] supported this etiology. A few questions, however, remain unanswered: is it proper to put all patients into the same category? When conservative treatment has failed, what is the proper treatment choice? To address these questions, we reviewed our experience with 19 cases of spontaneous hemarthrosis of the knee joint that were treated arthroscopically. We hypothesized that the cause of spontaneous recurrent hemarthrosis in the elderly could be attributed to a degeneratively torn lateral meniscus concomitant with lateral compartmental OA, and that lateral meniscectomy would be an adequate procedure when surgical treatment was necessary.

METHODS

Patients

Patients referred to our institution from affiliate hospitals because of recurrent hemarthrosis of the knee between April 1998 and October 2006 were involved in this retrospective study. Inclusion criteria were being over 40 years of age, the injury having no association with trauma, having no other findings other than OA changes on radiographic examination, and having no previous surgical treatment on the corresponding knee. Knees with obvious causes of hemarthrosis, such as pigmented villonodular synovitis, hemangioma, or other intra-articular abnormalities other than degenerative changes validated on magnetic resonance imaging (MRI) scans or at arthroscopy were excluded. Several items were recorded for each patient, including: (1) demographic information; (2) preoperative radiographic findings; (3) preoperative MRI findings; (4) arthroscopic findings and procedures performed; (5) the patient's medical history; and (6) the postoperative clinical course.

Radiographic Grading and Magnetic Resonance Imaging

All patients underwent radiographic imaging and MRI scans (Signa 1.5T; GE Yokokawa Medical Systems, Tokyo, Japan) of the affected knees. Radiographic grading with the Kellgren and Lawrence (KL) scale[7] was recorded for each compartment as follows: grade 0, no radiographic findings of osteoarthritis; grade 1, doubtful osteophyte formation; grade 2, definite osteophytes with unimpaired joint space; grade 3, definite osteophytes with moderate joint space narrowing; and grade 4, definite osteophytes with severe joint space narrowing and subchondral sclerosis. Among the 3 compartments, the OA compartment receiving the highest grade on the KL scale was considered the dominant osteoarthritic compartment. When the KL grade was the same for 2 or 3 compartments, a single author (K.N.), who had 19 years' experience in musculoskeletal radiology and was blinded to the clinical and arthroscopic information, determined the dominant osteoarthritic compartment according to degree of sclerosis and subchondral cysts formation. MRI was performed on fast spin echo, proton-weighted sagittal and coronal signals (TR 2000 ms, TE 16 ms, field of view 14 to 16 cm, matrix 512 $\times$ 256, number of excitations 2, and 3-mm slice thickness, without an interslice gap). Menisci were graded according to the scheme used by Crues et al.,[8] as follows: grade 0, normal; grade 1, intrameniscal focus of signal; grade 2, intrameniscal linear or wedge-shaped signal; and grade 3, linear or globular signal extending to an articular surface.

Operative Findings and Procedures

Arthroscopic findings and operative procedures were determined from operative records. A laser apparatus (VersaPulse; Coherent Japan, Tokyo, Japan) was used to coagulate bleeding points until the year 2003, and after that, a radiofrequency system (VAPR; DePuy Mitek, Raynham, MA) was used.

RESULTS

Patient Demographics

A total of 19 patients were enrolled in this study. Nine patients were male and 10 were female, with ages ranging from 41 to 83 years (mean, 61.9 yrs). On their first visit, all patients save for 1 had experienced aspiration of bloody joint fluid more than twice at affiliate hospitals. The average number of joint aspirations before surgery was 5.4 (range, 1 to 20 aspirations). The average time from onset to arthroscopy was 10 months (35 days to 8 yrs, 7 mos). Nine cases received arthroscopy within 3 months; 8 cases within 4 to 12 months; 1 case at 1 year and 2 months; and 1 case at 8 years and 7 months.

Preoperative Radiographic Findings and Magnetic Resonance Imaging

OA was diagnosed when the KL grade was found to be higher than 2. Two knees had isolated lateral compartment OA, 1 knee had isolated PF OA, 14 knees had medial and lateral compartment OA, and 2 knees had 3-compartment OA. Classifying knees according to the dominant compartment, 6 knees were medial-dominant OA, 11 were lateral-dominant OA, and 2 were PF-dominant OA.

Based on MRI scans, 18 lateral menisci were classified as grade III and the other was grade II. Eight medial menisci were grade II, 7 were grade I, and 4 were grade 0. Even with 6 medial-dominant OA, lateral meniscal involvement was more obvious than medial meniscal involvement on MRI.

Surgical Findings and Procedures Performed

Brown-colored diffuse synovitis in the knee was observed in all cases. Seventeen knees (89.5%) had degenerative torn lateral menisci (89.5%). Bucket handle–type tears were predominant (12 of 17), 3 were flap tears, and 2 were longitudinal tears. Among them, 6 were considered discoid lateral menisci because of their thicker rims and free margins. Two cases with PF-dominant OA (10.5%) did not have lateral meniscal injury. Two medial-dominant OA and a lateral dominant knee had degenerative torn medial menisci at the posterior segment. All 3 tears were horizontal and did not exceed half width of the meniscal body; trimming of the free margin was performed for these lesions.

In 17 torn lateral meniscus cases, hypertrophy of synovium around the rim of the lateral meniscus was observed. Subtotal meniscectomy was performed on these 17 cases, and bleeding from the lateral meniscus around the popliteus tendon was observed in the process of debridement in 16 cases. For 2 PF OA cases, synovectomy using VAPR and a histologic examination of synovium were performed.

Medical History

Eleven patients did not have any history of other diseases. Hypertension was found in 7 patients. Among them, 1 patient was taking an anticoagulant because of a transient ischemic attack. One patient had an elongation of bleeding time caused by late-stage liver cirrhosis.

Postoperative Course

Recurrence of hemarthrosis after arthroscopic surgery was found in the single case with liver cirrhosis (5.3%). The other 18 patients have not had a recurrence of hemarthrosis for an average of 5 years and 2 months (1 yr, 10 mos to 9 yrs, 7 mos).

Case 1

A 65-year-old woman had been suffering from left knee pain for about 10 years. She felt severe knee pain without any traumatic episode, went to a hospital, and received arthrocentesis that produced 40 mL of bloody joint flood. Her knee pain was relieved by this arthrocentesis. After that, she experienced similar episodes 7 times in 3 months and was referred to our hospital. Because of the sudden onset of hemarthrosis and severe pain, her chief complaint was fear and apprehension about knee pain and swelling. Her radiographic findings revealed KL grade 3 lateral type OA with KL grade 2 medial compartment (Fig 1), and MRI scans showed a degenerative torn lateral meniscus (Fig 2). Arthroscopy was performed and revealed a degenerative torn lateral meniscus. Removal of a small meniscal segment induced pulsatile bleeding from the residual rim of the lateral meniscus. We

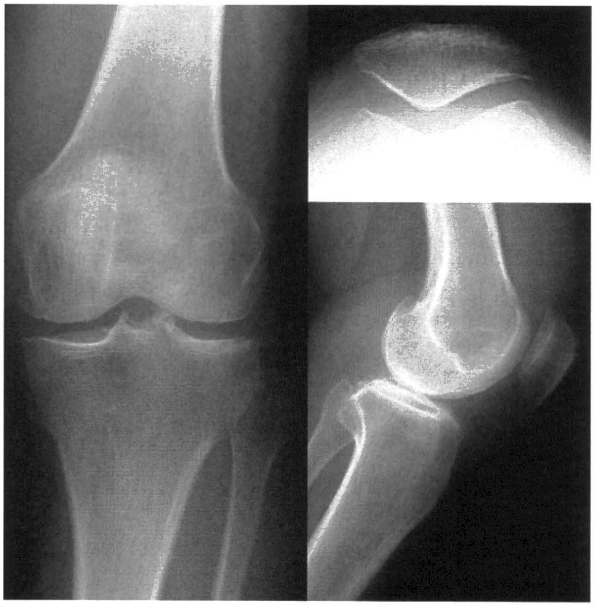

FIGURE 1. Radiographic findings of case 1 (a 65-year-old woman). An anteroposterior radiograph reveals lateral-dominant osteoarthritis along with involvement of the medial compartment (left) and minimum involvement of osteoarthritic changes of the patellofemoral joint (upper right and lower right).

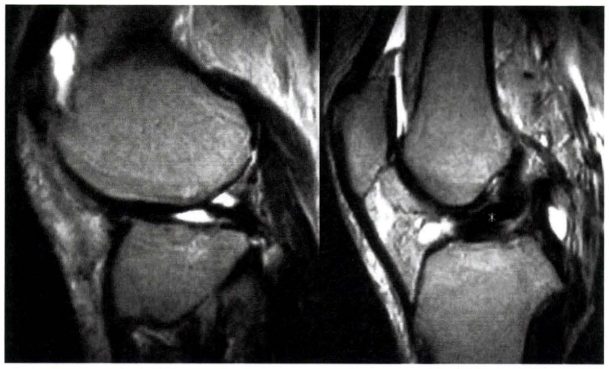

FIGURE 2. Magnetic resonance imaging findings of case 1. The irregularly shaped triangle of the posterior horn indicates torn lateral meniscus. The lack of cartilage is obvious on both the femoral and tibial surfaces in the lateral compartment (left). Dislocated lateral meniscal fragment can be seen adjacent to the anterior cruciate ligament (right, asterisk).

performed a subtotal meniscectomy with air tourniquet followed by coagulation using VAPR without air tourniquet (Fig 3). No recurrence has been observed for more than 2 years.

Case 2

An 83-year-old woman received arthrocentesis 6 times in 9 months, which produced bloody joint fluid each time, before referral to our hospital. Her chief complaint was fear and apprehension about the recurrence of hemarthrosis. Her radiographic findings exhibited KL grade 2 OA involvement of the PF joint (Fig 4). Arthroscopy was performed. A diffuse proliferation of brown synovium was observed, and a tumorous lesion was found floating in the suprapatellar pouch with no connection to the joint capsule (Fig 5). A pathologic examination found that this lesion was a hematoma in its process of organization (Fig 6). Arthroscopic synovectomy was performed.

DISCUSSION

Spontaneous hemarthrosis of the knee is a relatively rare condition observed in older OA patients. In 1959, Wilson[1] reported 5 cases of spontaneous hemarthrosis in OA knees. He suggested a vascular fringe of synovial membrane around the deformed patella as a cause of hemarthrosis because of the high prevalence of retropatellar arthritis in patient radiographs. A successful outcome of conservative treatment was also reported. In 1964, Burman et al.[2] reported that synovectomy accompanied with medial and lateral meniscectomy was successful. Morii et al.[3] also reported successful outcomes for 16 patients who received synovectomy, although only 7 knees received synnovectomy alone, and the other 9 knees were treated with several other accompanying procedures.

Until 1991, synovium had been considered to be the origin of bleeding; therefore, synovectomy appeared to be the most reasonable treatment. But in 1994, Kawamura et al.[4] suggested that the cause of this hemarthrosis was most likely the peripheral arteries of the posterior horn of the lateral meniscus. They underwent arthroscopic resection of the posterior portion of the remaining degenerative lateral meniscus and achieved satisfactory results. Pellacci et al.[5] also achieved successful outcomes with total lateral meniscectomy. Ogawa et al.[6] reported a case of recurrent

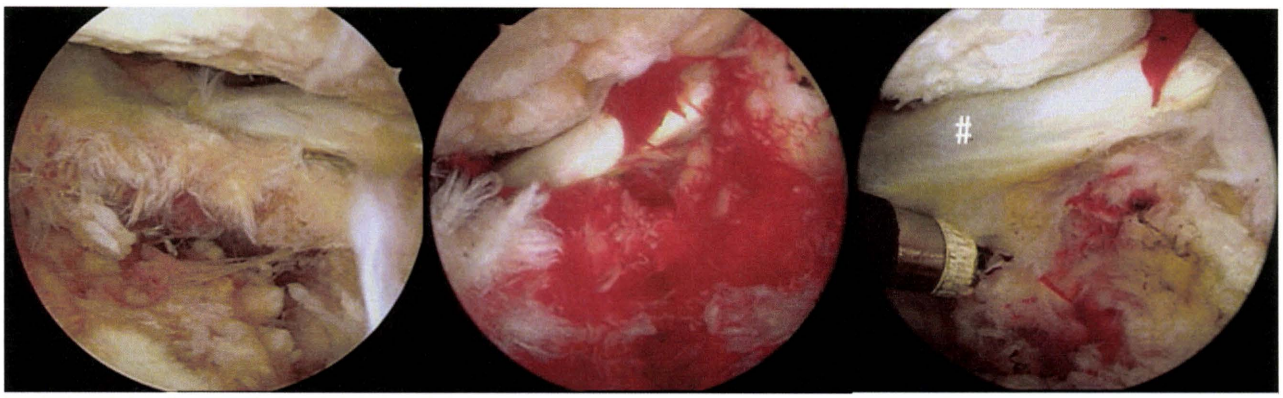

FIGURE 3. Arthroscopic treatment of case 1. The degenerative torn lateral meniscal rim is present between the femoral and tibial surfaces that are covered with patchy fibrous cartilage (left). The removal of a small meniscal segment induces pulsatile bleeding from the residual rim of the lateral meniscus (middle). Subtotal meniscectomy followed by coagulation using VAPR was performed (right). Note that nothing but the popliteus tendon can be seen in the lateral compartment (right, number sign).

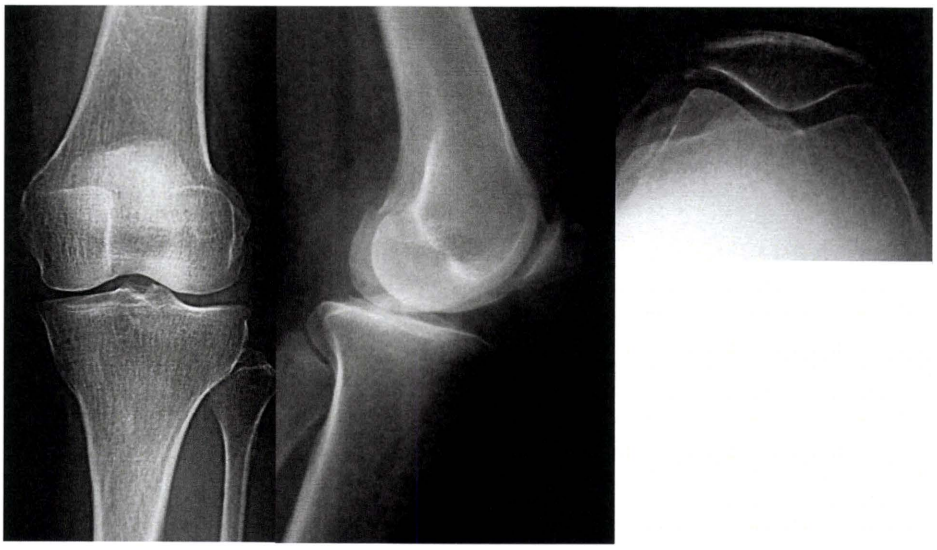

FIGURE 4. Radiographic findings of case 2 (an 83-year-old woman) showing no arthritic changes in the tibiofemoral joint (left) and slight osteoarthritic involvement of the patellofemoral joint (middle and right).

hemarthrosis associated with meniscal ganglion and treated with resection of the lateral meniscus and meniscal ganglion, speculating that the torn lateral meniscus caused the bleeding. From our experience, a majority of the patients (17 of 19) had degenerative torn lateral menisci as determined with MRI and at arthroscopy. The mostly successful treatment was meniscectomy and coagulation using a laser or radiofrequency system. A majority of so-called spontaneous recurrent hemarthroses of the knee in the elderly appear to be attributable to torn lateral menisci. Recurrent hemarthrosis of the knee caused by degenerative torn lateral meniscus or meniscogenic recurrent hemarthrosis (MRH) could be legitimate names for this condition. A small portion of patients might be suffering from bleeding from synovium, possibly around the PF joint, as Wilson speculated,[1] and only this condition should be called spontaneous recurrent hemarthrosis (SRH) of the knee in the elderly.

Considering that recurrent hemarthrosis occurs only in older patients, a combination of other factors, such as age-related mechanical and structural changes of vessels,[9-11] may also be necessary for this condition. The relatively high percentage of patients with hypertension in this case series might enhance these changes.[12,13]

As a treatment option, we recommend subtotal meniscectomy and coagulation using a radiofrequency system for MRH cases. For SRH cases, we are not positive that arthroscopic synovectomy is an effective treatment, because we could not detect a bleeding point arthroscopically. Two out of two SRH patients have not experienced hemarthrosis for more than 6 years after arthroscopy.

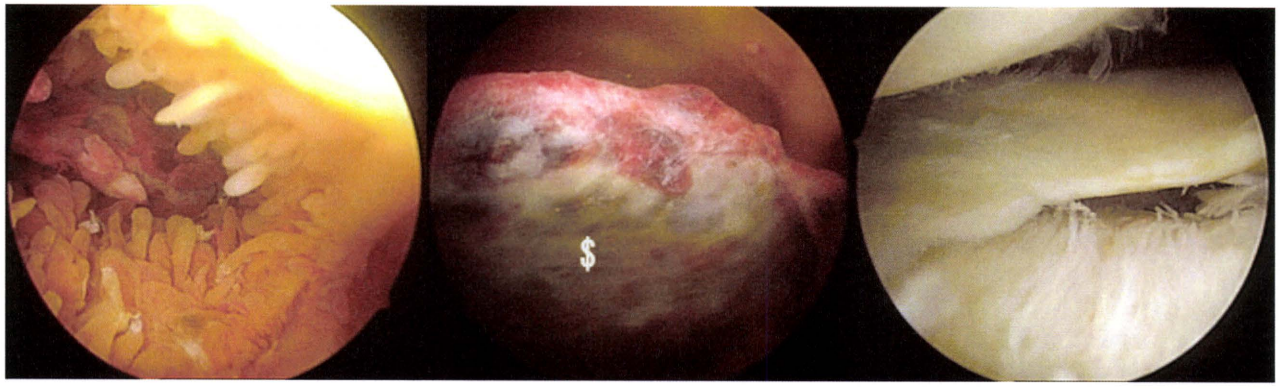

FIGURE 5. Arthroscopic treatment for case 2. Diffuse proliferation of brown synovium can be seen (left). A tumorous lesion can be seen in the suprapatellar pouch that is floating in the pouch with no connection to the joint capsule (middle, dollar sign). The lateral meniscus has surface fibrillation without tears (right).

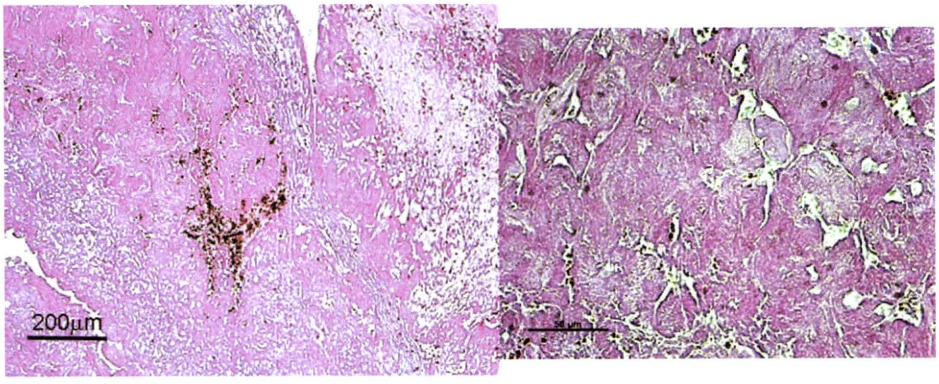

FIGURE 6. H&E staining of the tumorous lesion in case 2 reveals a hematoma in the process of organization. The paucity of cellularity and abundant collagenous tissue are the main constituents of the lesion. Areas of hemosiderin deposition can also be seen. (Left: ×100; right: ×320.)

Considering that they had received arthrocentesis on about a once-a-month basis before surgery, arthroscopic synovectomy could be called a curative treatment. Therefore, arthroscopic synovectomy is a promising treatment, but it might be possible that the lesions are self-limiting conditions where conservative treatment might have given satisfactory results. Another possibility is that with arthroscopy or MRI, we could not detect intra-articular lesions that may lead to hemarthrosis, such as hemangioma or localized type pigmented villonodular synovitis, and these were removed coincidently upon synovectomy.

It is known that medial-dominant OA is more predominant in the population than lateral-dominant OA,[14] but in the present case series, most of the patients had lateral-dominant OA. Even with 6 cases of medial-dominant OA, they had OA changes in their lateral compartment, and torn lateral menisci were the most apparent arthroscopic findings. Therefore, the existence of OA changes in the lateral compartment is considered a typical radiographic finding of MRH. Pre-existing discoid lateral menisci might be a risk factor for MRH, because 6 of 17 cases had discoid lateral menisci. We have not yet identified why degenerative torn lateral meniscus but not medial meniscus exclusively causes hemarthrosis. Possible explanations for this disparity are the size difference of vascularity and different positional relationship between the genicular artery and the menisci. The lateral inferior and middle genicular arteries that supply the lateral meniscus are much larger than the medial genicular artery.[15] The proximity of the genicular artery to the meniscal rim is observed only on the lateral meniscus.[16] In the present study, throbbing bleeding indicting arterial bleeding was observed in the process of debridement of lateral menisci in 5 cases, which suggested direct bleeding from the lateral genicular artery. Negative pressure during knee motion, especially at the mid-flexion angle, might enhance bleeding and prevent coagulation.[17]

A couple of limitations should be noted. The small number of cases might not have been enough to describe the detailed etiology of the disease. But even with only 19 cases, this study appears to be the biggest surgically treated case series in the literature. Involvement of only arthroscopically treated cases might also be another limitation. The inclusion of conservatively treated cases might aid in the comprehension of a complete picture of the disease.

CONCLUSIONS

A majority of the patients (17 of 19) had degenerative torn lateral menisci confirmed with MRI and at arthroscopy. Successful outcomes were achieved by meniscectomy and coagulation. Most so-called spontaneous recurrent hemarthroses in OA knee joints appear to be attributable to torn lateral menisci.

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Original article

RGD peptide-induced cell death of chondrocytes and synovial cells

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Abstract

Background. Small peptides including the Arg-Gly-Asp (RGD) motif have been used in studies on cell-extracellular matrix (ECM) attachment due to their ability to disturb integrin-mediated attachment on the cell surface. As another biological action of RGD peptides, several reports have shown that RGD peptides are incorporated into cytoplasm and induce apoptosis by direct activation of caspase-3. This study evaluated the effect of RGD peptides on chondrocytes and synovial cells and studied the involvement of caspases.

Methods. Chondrocytes and synovial cells were isolated and cultured from the knee joints of New Zealand White rabbits. Cells were incubated in serum-free medium with peptides (RGD, RGDS, GRGDSP, GRGDNP, RGES), and the survival rates were evaluated. The rate of apoptotic cells was measured by flow cytometry in cells treated with RGDS, GRGDSP, and RGES. Caspase-3, -8 and -9 activity was measured in cells treated with RGDS and GRGDSP. Osteochondral explants harvested from rabbits were also incubated with RGD peptides (RGDS, GRGDSP, and GRGDNP), and the survival rate of chondrocytes was evaluated.

Results. The survival rate of cultured chondrocytes was significantly decreased in the GRGDSP- and GRGDNP-treated groups. The survival rate of synovial cells was significantly decreased with four of the RGD peptides (RGD, RGDS, GRGDSP, and GRGDNP) at 5 mM, and in the RGDS- and GRGDSP-treated groups at 1 mM. Flow cytometric assay revealed increases of apoptotic chondrocytes with GRGDSP and increases of apoptotic synovial cells with RGDS and GRGDSP. Caspase-3 was activated in chondrocytes treated with GRGDSP and it was also activated in synovial cells treated with RGDS and GRGDSP. Caspases-8 and -9 were not activated in chondrocytes or in synovial cells. The survival rate of chondrocytes in explants decreased in the superficial layer with all three RGD peptides (RGDS, GRGDSP, and GRGDNP) and in the middle layer with GRGDSP.

Conclusions. RGD peptides induced apoptosis in cultured chondrocytes as well as in cells in cartilage explants and synovial cells, presumably through direct activation of caspase-3.

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Introduction

Small peptides including the arginine-glycine-aspartate (RGD) motif are present in the extracellular matrix (ECM) and work as ligands for integrins.[1] Thus, RGD peptides have been used in studies on cell-ECM attachment due to their ability to disturb integrin-mediated attachment.[2,3] Cell attachment is crucial for cell survival in a variety of cells; therefore, adhesion-blocking agents, including RGD peptides, cause caspase-dependent apoptotic cell death, known as anoikis.[4] However, Buckley et al.[5] reported that RGD peptides were incorporated into cytoplasm and induced apoptotic cell death in lymphocytes through direct activation of caspase-3.

Caspases are a family of cysteine proteases that cleave their substrates at aspartate residues and play key roles in apoptosis.[6] Caspases exist in cells as catalytically inactive zymogens, referred to as procaspases.[7] Once activated, most caspases can process and activate themselves and other inactive procaspases. This characteristic suggests that caspases may execute the apoptotic program through a cascade of sequential activation of initiators, such as caspases-8 and -9, and executioners, such as caspases-3 and -7.[8]

The purpose of this study was to evaluate the effect of RGD peptides on cells in two major components of joint disease, cartilage and synovium. Specifically, the effect of RGD peptides to induce cell death was examined. Apoptotic cell death is one of the major factors in the progression or initiation of osteoarthritis (OA). Synovial cell proliferation is a typical feature of arthritic diseases. Knowledge of differences in the susceptibility to RGD peptides between chondrocytes and synovial

cells might be clinically useful in treating synovial proliferating diseases, or in creating a new osteoarthritic animal model. Thus, we first examined induction of cell death in cultured chondrocytes and synovial cells by RGD peptides, followed by examination of caspase involvement and annexin V induction in the pathway leading to cell death. Last, we examined the induction of cell death in chondrocytes in osteochondral explants by RGD peptides.

Materials and methods

Experiments were conducted in accordance with the guidelines for animal experimentation of the Ethics Review Committee of Chiba University.

RGD peptides

Four kinds of RGD peptides: i.e., RGD (Arg-Gly-Asp), RGDS (RGD-Ser), GRGDSP (Gly-RGDS-Pro), and GRGDNP (GRGD-Asn-P), and non-RGD peptide RGES (RG-Glu-S), were purchased (Funakoshi, Tokyo, Japan). Stock solutions (50 mM) were prepared by dissolving the peptides in phosphate buffered saline (PBS; Gibco, Grand Island, NY, USA) and stored at –20°C. RGDS peptide labeled with fluorescein isothiocyanate (FITC; Funakoshi) was also prepared as a 50-mM stock solution.

Cell culture

Cartilage and synovium were harvested from the knee joints of 1-month-old New Zealand White rabbits. Chondrocytes were isolated by an enzymatic preparation. Briefly, cartilage specimens were minced and washed with PBS. The specimens were then treated with 0.05% hyaluronidase (Sigma-Aldrich, St Louis, MO, USA) at 37°C for 10 min and 0.2% trypsin (Wako, Osaka, Japan) for 15 min, followed by digestion with 0.2% collagenase (Asahi Techno Glass, Tokyo, Japan) for 1 h. Isolated chondrocytes were collected by centrifugation (1500 rpm, 10 min) and washed with PBS. Then they were suspended in Dulbecco's modified Eagle's medium (DMEM; Gibco) supplemented with 10% heat-inactivated fetal bovine serum (FBS; Gibco), 2 mM of L-glutamine (Gibco) and antibiotics consisting of penicillin G sodium and streptomycin sulfate (Gibco), and incubated at 37°C.

Synovial cells were isolated by enzymatic digestion as described previously.[9] Briefly, synovial tissues were minced and digested with Dispase Grade II (Roche Diagnostics, Indianapolis, IN, USA) for 2 h at 37°C. Isolated synovial cells were collected and washed with PBS. The cells were then seeded in RPMI1640 (Gibco) containing 10% FBS and antibiotics and incubated at 37°C.

Cells were cultured to first or second passage until cells increased sufficiently for analysis.

Viability of cultured cells

Chondrocytes and synovial cells were collected and resuspended at a density of 2×10^5 cells/ml in a 12-well plate with serum-free medium and incubated for 48 h at 37°C with 1 or 5 mM of peptides, i.e., RGD, RGDS, GRGDSP, GRGDNP, and RGES. Concentrations of peptides were determined according to previous reports.[5,10] Control cells were incubated in medium that did not contain any peptides. For detection of cell death, the Live/Dead Double Staining Kit (MBL, Nagoya, Japan) was used, following the manufacturer's instructions. Briefly, cells were collected and resuspended in staining solution containing 1 μM of CYTO-Dye (MBL, Nagoya, Japan), a cell-permeable green fluorescent dye, and 2.5 μg/ml of propidium iodide (PI), a cell nonpermeable red fluorescent dye, and incubated for 15 min at 37°C. Live cells were stained only with the CYTO-Dye and dead cells were stained with both CYTO-Dye and PI. The numbers of live and dead cells from each specimen were counted under a fluorescence microscope (Nikon, Tokyo, Japan) until the total cell number reached 100 cells in randomly selected fields of view. Survival rate was expressed as the percentage of live cells.

Flow cytometric analysis with Annexin V-FITC

Chondrocytes and synovial cells were harvested from five knee joints of New Zealand White rabbits. The cells were collected and resuspended at a density of 2×10^5 cells/ml in a 12-well plate with serum-free medium supplemented with 5 mM of peptides (RGDS, GRGDSP, and RGES). Cells were then incubated for 4 h at 37°C. Control cells were incubated in medium that did not contain any RGD peptides. A MEBCYTO apoptosis kit (MBL, Nagoya, Japan) was used for detection of apoptosis, according to the manufacturer's instructions. Briefly, the collected cells were washed and resuspended in 85 μl of binding buffer. Then, 10 μl of Annexin V-fluorescein isothiocyanate (FITC) and 5 μl of PI were added. After 15-min incubation at room temperature, the cells were counted with a FACScan cytometer (Beckton-Dickinson, San Diego, CA, USA) up to 5000 cells. The percentages of apoptotic cells in the total number of cells were calculated and were used for analysis.

Treatment of cells with FITC-labeled RGD peptide

To examine the localization of RGD peptides, cultured chondrocytes and synovial cells were collected and resuspended in serum-free medium supplemented with

5 mM FITC-labeled RGDS and incubated at 37°C. After 2 h, the cells were evaluated with a fluorescence microscope.

Caspase activity assay

Cultured cells were collected and resuspended at a density of 1×10^6 cells/ml in a 6-well plate with serum-free medium supplemented with 1 or 5 mM of RGD peptides (RGDS and GRGDSP). Cells were then incubated for 4 or 24 h at 37°C. Control cells were incubated in medium that did not contain any RGD peptides. After 4 or 24 h, intracellular caspase-3, -8, and -9 activity was measured with the APOPCYTO colorimetric assay kit (MBL) according to the manufacturer's instructions. Briefly, the cells were collected and resuspended in cell lysis buffer for 10 min. The cell lysates were centrifuged at 10000 *g* for 5 min at 4°C and the supernatants were obtained. Then, 50 µl of reaction buffer containing 10 mM dithiothreitol (DTT), 50 µl of cell lysates, and 5 µl of caspase substrates were added to each well of a 96-well microplate and incubated overnight at 37°C. These substrates were labeled with p-nitroanilide (pNA); i.e., DEVD-pNA for caspase-3, IETD-pNA for caspase-8, and LEHD-pNA for caspase-9. When substrates were recognized and cleaved by the corresponding caspases, pNA was released. Caspase activity was calculated by measuring the amount of free pNA at a wavelength of 405 nm with a microplate reader (Asahi Techno Glass, Tokyo, Japan).

Viability of chondrocytes in osteochondral explants

The bilateral proximal epiphyses of the tibiae (osteochondral explants) were harvested from four 15-month-old New Zealand White rabbits at a thickness of 5 mm horizontally. Special care was taken not to touch the cartilage surface. The explants were cultured in serum-free DMEM supplemented with 5 mM of RGD peptides (RGDS, GRGDSP, or GRGDNP). Control specimens were cultured without any peptides. After 48 h, two 1-mm-wide pieces of cartilage that were vertical to the joint surface were cut out from each condyle and stained with the Live/Dead Double Staining Kit (MBL). Cell viability of the superficial and middle layer was assessed separately with a confocal microscope (Carl Zeiss, Heidelberg, Germany). The deep layer was excluded in this study, because cells in the deep layer might have been affected at the time of cartilage preparation, i.e., necrotic cell death might have occurred at the bottom of cartilage when the cells were separated from the underlying subchondral plate. The survival rate of chondrocytes was determined by manual counting.

Statistical analysis

Values for results were expressed as the mean plus or minus standard deviation (SD). Statistical comparisons were done with the paired *t*-test. A significant difference was set at a level of $P < 0.05$.

Results

Viability of cultured cells

Representative images of RGD peptide-treated chondrocytes stained using the Live/Dead Double staining Kit are shown in Fig. 1A, where dead cells are stained yellow and live cells are stained green. The survival rate of chondrocytes was significantly decreased with both 1 mM and 5 mM GRGDSP and GRGDNP, compared to control (Fig. 1B). These two peptides induced cell death in more than 30% of chondrocytes. By contrast, dead cells accounted for less than 20% of RGES-treated cells and control cells. With 5 mM RGDS the survival rate (70.8 ± 6.1%) tended to be low, but this difference was not significant ($P = 0.052$).

The survival rate of synovial cells was significantly decreased with four of the RGD peptides at 5 mM (Fig. 1C, RGD, 65.0 ± 12.1%; RGDS, 65.3 ± 12.9%; GRGDSP, 60.9 ± 13.1%; and GRGDNP, 66.4 ± 6.9%), compared to RGES-treated cells and control cells. However, the survival rate at 1 mM was significantly decreased in only the RGDS and GRGDSP groups (58.8 ± 10.8% and 60.0 ± 15.3%, respectively). The difference in survival rates between 1 and 5 mM concentrations of these two peptides was not significant.

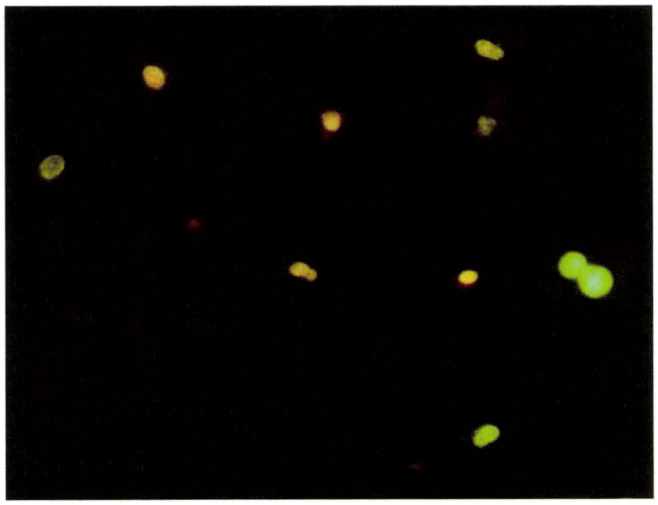
Flow cytometric analysis by Annexin V-FITC

The representative result of FACScan is shown in Fig. 2A. The percentage of apoptotic cells in chondrocytes treated with GRGDSP was significantly higher than that in RGES-treated cells and control cells (Fig. 2B; 7.00 ± 4.27%, 3.06 ± 1.75%, and 3.68 ± 2.05%, respectively). However, significant apoptotic cell death was not observed in the cells treated with RGDS (5.39 ± 2.03%).

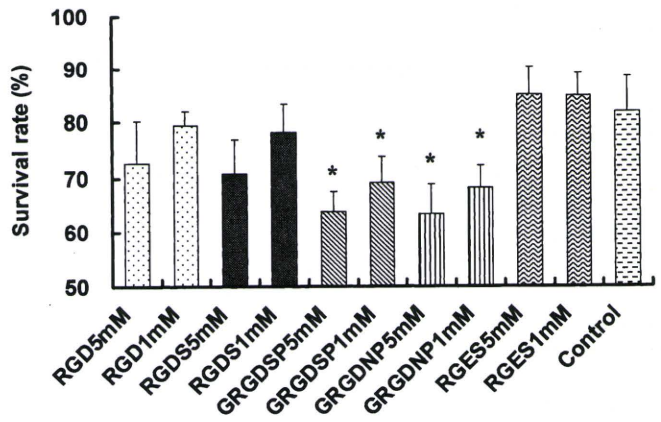
The percentages of apoptotic cells in synovial cells treated with RGDS and GRGDSP were significantly higher than those in RGES-treated cells and control cells (Fig. 2C; 14.8 ± 5.46%, 10.8 ± 2.15%, 3.27 ± 1.93%, and 3.73 ± 0.87%, respectively).

Localization of RGD peptide

FITC-labeled RGDS peptide was used to determine the location of RGD peptide in chondrocytes and synovial cells. The labeled peptides were found in the cytoplasm and not on the cell surface in both chondrocytes and



A



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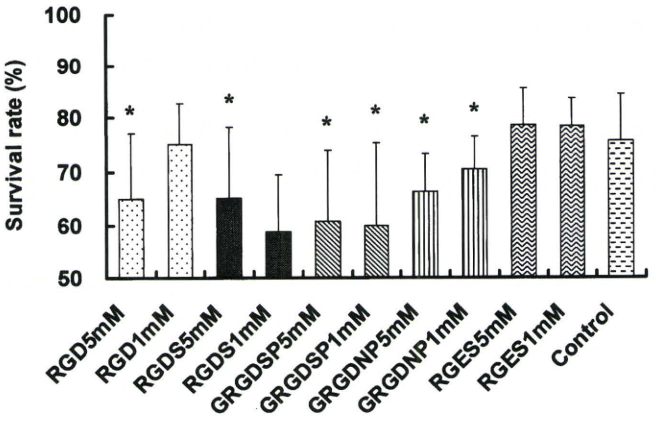


C

Fig. 1A–C. Effect of Arg-Gly-Asp motif (RGD) peptides on the viability of cultured chondrocytes and synovial cells. Cells were incubated in serum-free medium supplemented with 1 or 5 mM RGD, RGDS, GRGDSP, GRGDNP, and RGES for 48 h. Survival rate was expressed as the percentage of live cells. **A** Fluorescence microscopy of chondrocytes treated with 5 mM GRGDSP and stained using the Live/Dead Double Staining Kit (MBL). Live cells were stained only with CYTO-Dye (MBL), and dead cells were stained with both CYTO-Dye and propidium iodide (PI). Thus, the dead cells were seen in *yellow* in a merged image. **B** Viability of cultured chondrocytes. The viability was significantly decreased in cells treated with 1 and 5 mM GRGDSP and GRGDNP. **C** Viability of cultured synovial cells. The viability was significantly decreased in cells treated with 5 mM of four of the five peptides and in cells treated with 1 mM of RGDS and GRGDSP. Results are shown as means and SD; $n = 5$. The value of $*P < 0.05$ was considered significant when compared to RGES-treated cells and control. **A**, × 100

synovial cells. The labeled peptide was incorporated into the cytoplasm, but not the nucleus (Fig. 3).

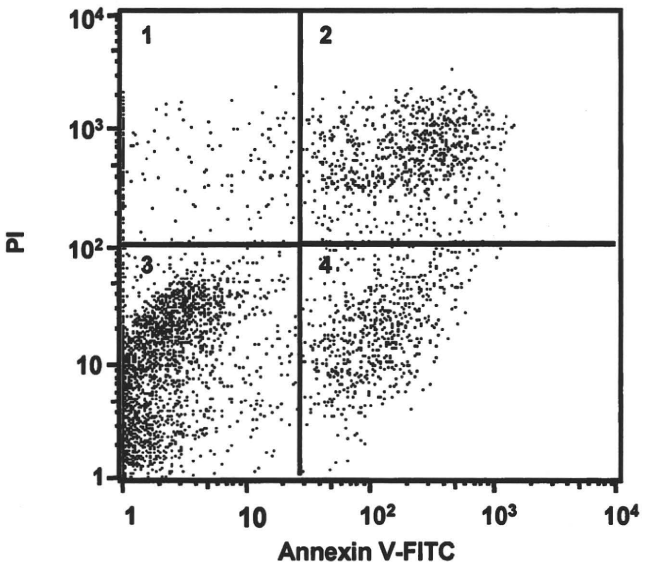
Caspase activity induced by RGD peptides

The activity of caspase-3 was significantly elevated in chondrocytes treated with 5 mM GRGDSP for 4 h compared to control (Fig. 4A; 215 ± 74 μM pNA and 32.7 ± 6.9 μM pNA, respectively). However, no significant activation of caspase-8 and -9 was detected in chondrocytes.

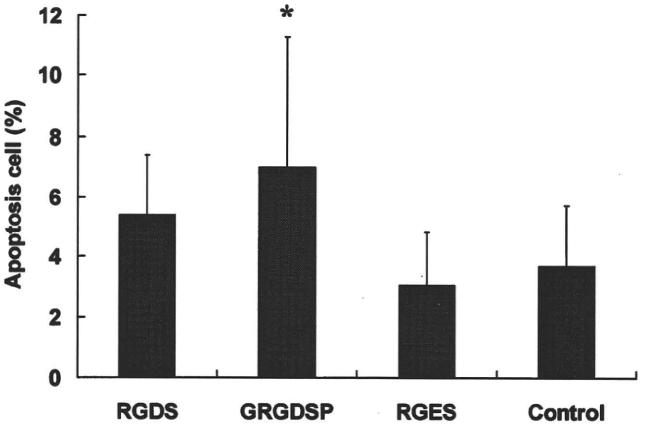
The activity of caspase-3 was significantly elevated in synovial cells treated with 5 mM RGDS and GRGDSP for 4 h compared to control (Fig. 4B, 143 ± 64 μM pNA, 210 ± 107 μM pNA, and 48.6 ± 12.7 μM pNA, respectively). However, the activity of caspases-8 and -9 in synovial cells was not elevated.

The activity of caspase-3 was significantly elevated in chondrocytes treated with 1 mM GRGDSP for 24 h compared to control (Fig. 4C, 57.3 ± 3.1 μM pNA and 35.4 ± 11.5 μM pNA, respectively). However caspases-8 and -9 were not activated.

The activity of caspase-3 was significantly elevated in synovial cells treated with 1 mM RGDS or GRGDSP for 24 h compared to control (Fig. 4D, 133 ± 16 μM pNA, 155 ± 43 μM pNA, and 87.0 ± 22.0 μM pNA, respectively). However caspases-8 and -9 were not activated.



A



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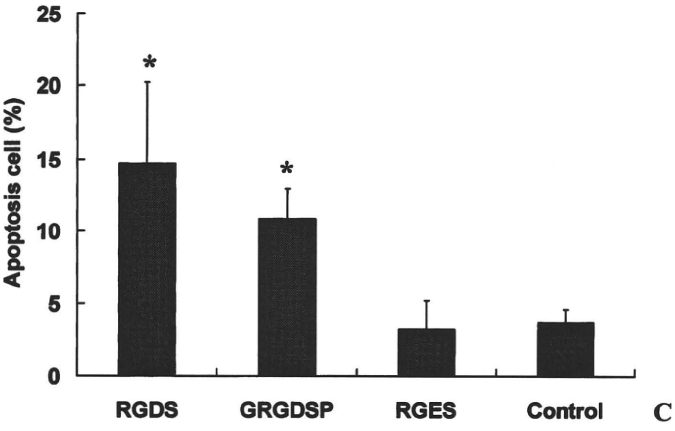

C

Fig. 2A–C. Flow cytometric analysis with Annexin V-fluorescein isothiocyanate (FITC). Cells were incubated in serum-free medium supplemented with 5 mM of RGDS, GRGDSP, and RGES for 4 h. Then, cells were treated with the MEBCYTO apoptosis kit (MBL) and analyzed with a FACScan cytometer (Beckton-Dickinson). **A** Representative result of FACScan (synovial cells treated with RGDS). *Quadrants 2, 3, and 4* represent necrotic cells, live cells, and apoptotic cells, respectively. In this case, the percentage of apoptotic cells was 11.8%. **B** The percentage of apoptotic cells in chondrocytes ($n = 5$). The percentage of apoptotic cells was significantly higher in the cells treated with GRGDSP, compared to RGES-treated cells and control. **C** The percentage of apoptotic cells in synovial cells ($n = 4$). The percentage of apoptotic cells was significantly higher in the cells treated with both RGDS and GRGDSP, compared to RGES-treated cells and control. Results are shown as means and SD. The value of $^*P < 0.05$ was considered significant when compared to RGES-treated cells and control

Viability of chondrocytes in osteochondral explants

A confocal microscopic image of an osteochondral explant treated with RGD peptide is shown in Fig. 5A. There was no difference in survival rate between the medial and the lateral condyle (data not shown). The survival rate in the superficial layer was significantly decreased in cartilage treated with all three RGD peptides (Fig. 6; RGDS, 76.5 ± 5.2%; GRGDSP, 77.3 ± 4.1%; and GRGDNP, 78.8 ± 12.2%), compared to control (95.0 ± 2.9%). In the middle layer the survival rate was significantly decreased in the GRGDSP-treated group only (79.8 ± 3.6%). There was no significant difference in survival rates between the superficial and middle layer.

Discussion

RGD peptide-induced apoptotic cell death and its pathway

The present study demonstrated that RGD peptides were incorporated into the cytoplasm of both chondro-

cytes and synovial cells, and they induced cell death by activating caspase-3, presumably not by disturbing integrin-mediated attachment on the cell surface (anoikis). The cell death pathway appeared to be the same in both types of cells, where caspases-8 and -9 were skipped and caspase-3 was directly activated. In the caspase activity assay, only caspase-3 was highly activated, while caspases-8 and -9 were inactive after 4-h and 24-h incubation with RGD peptides. Although we presented data at only two time points, this finding implied that caspase-3 was the only caspase that was activated by RGD peptide in the first 24 h, because previous studies demonstrated that elevated activities of caspases induced by administering RGD peptide persisted for more than 24 h.[11,12] Buckley et al.[5] reported that RGD peptides bound to a DDM sequence of procaspase-3 and promoted auto-processing to activate caspase-3 in lymphocytes. The same mechanism could be operating in chondrocytes and synovial cells. On the other hand, Aguzzi et al.[13] suggested that RGDS peptide induced early activation of caspases-8 and -9 with 4-h treatment and late activation of caspase-3 with 24-h treatment in endothelial cells. Caspases-8 and -9 are thought to be activated prior to caspase-3 in the caspase cascade.[14] The difference in cell type might explain the difference in the manner of caspase-3 activation.

No previous report has examined the effect of RGD peptides on chondrocytes in an explant system. According to the results with cultured chondrocytes, we

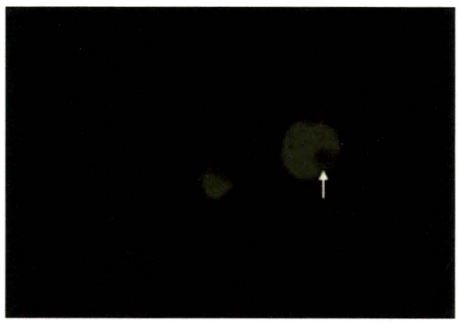

Fig. 3. Fluorescence microscopy of synovial cells treated with FITC-labeled RGDS. Cells were incubated in serum-free medium supplemented with 5 mM of peptide for 2 h. The fluorescence was confined to the cytoplasm, while the nucleus was void of the labeled peptides (*arrow*). × 100

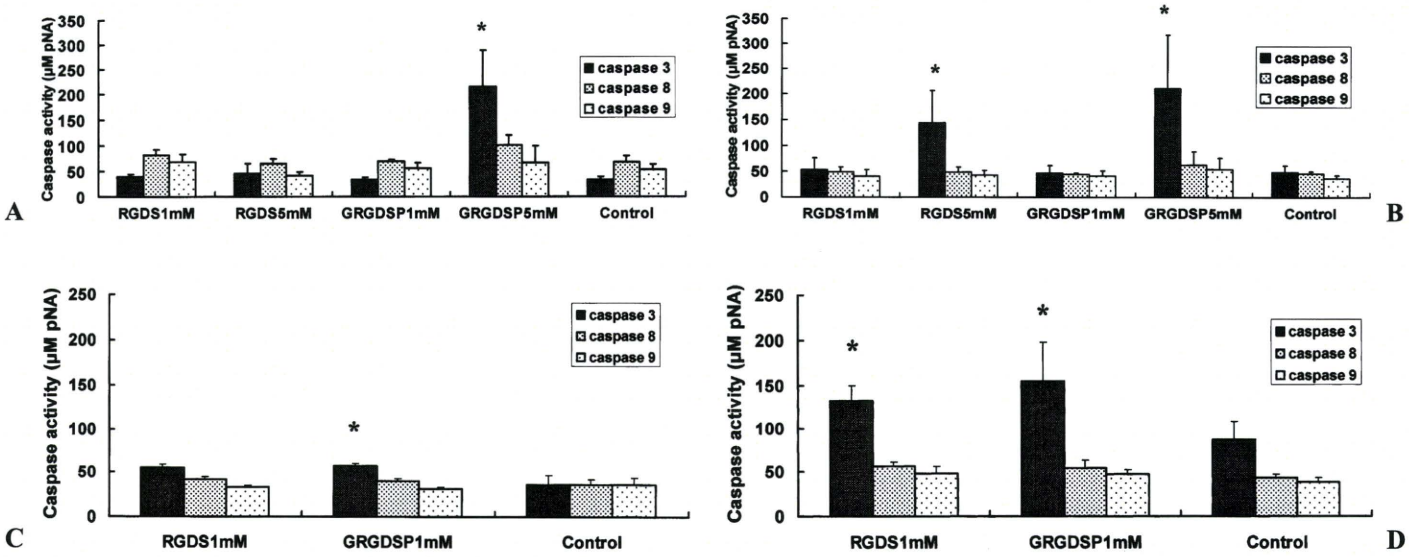

Fig. 4A–D. Effect of RGD peptides on caspase activity. Cells were incubated in serum-free medium supplemented with 1 or 5 mM of RGDS and GRGDSP for 4 or 24 h. The activity of caspases-3, -8, and -9 was measured with the APOPCYTO (MBL) colorimetric assay kit. Caspase activity was calculated by measuring the amount of free p-nitroanilide (pNA) released from the substrates with a microplate reader. **A** Activity of caspases-3, -8, and -9 in chondrocytes after 4-h treatment. The activity of caspase-3 was significantly elevated in the cells treated with 5 mM of GRGDSP, compared to control. The activity of caspases-8 and -9 was not elevated in cells treated with any of the peptides. **B** Activity of caspases-3, -8, and -9 in synovial cells after 4-h treatment. The activity of caspase-3 was significantly elevated in the cells treated with 5 mM of RGDS and GRGDSP, compared to control. The activity of caspases-8 and -9 was not elevated in cells treated with any of the peptides. **C** Activity of caspases-3, -8, and -9 in chondrocytes after 24-h treatment. The activity of caspase-3 was significantly elevated in the cells treated with 1 mM of GRGDSP, compared to control. The activity of caspases-8 and -9 was not elevated in cells treated with any of the peptides. **D** Activity of caspases-3, -8, and -9 in synovial cells after 24-h treatment. The activity of caspase-3 was significantly elevated in the cells treated with 1 mM of RGDS and GRGDSP, compared to control. The activity of caspases-8 and -9 was not elevated in cells treated with any of the peptides. Results are shown as means and SD; $n = 4$. The value of $^*P < 0.05$ was considered significant when compared to control

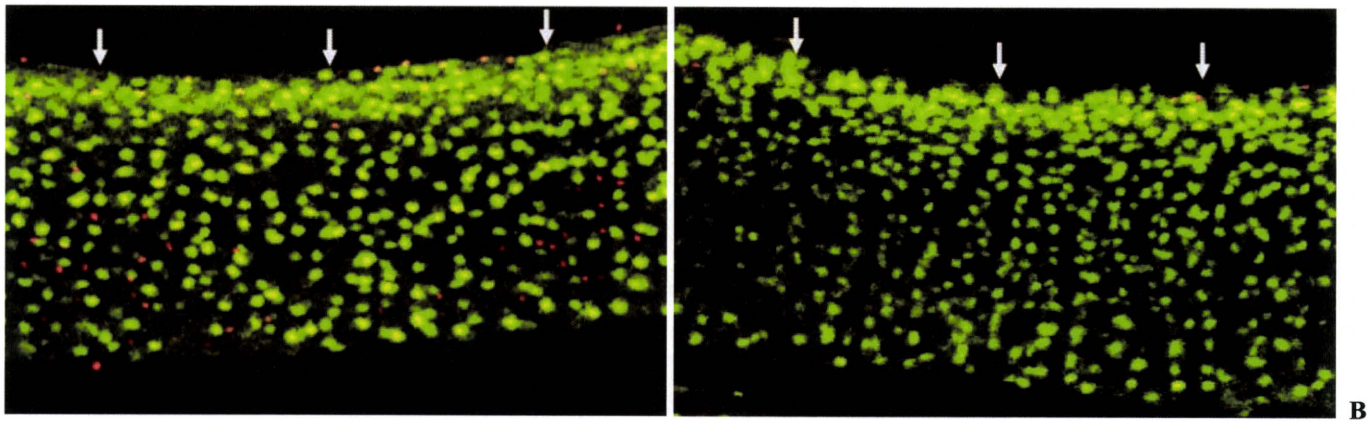

Fig. 5A,B. Confocal microscopy of cartilage stained using the Live/Dead Double Staining Kit (MBL). Live cells are stained *green* and dead cells are seen in *yellow*. *Arrows* indicate the surface of cartilage. **A** Cartilage harvested from lateral condyle of tibia treated with 5 mM of GRGDSP. Dead cells are seen in both the superficial and middle layers. **B** Control cartilage from lateral condyle. Very few dead cells are observed. **A** and **B** × 50

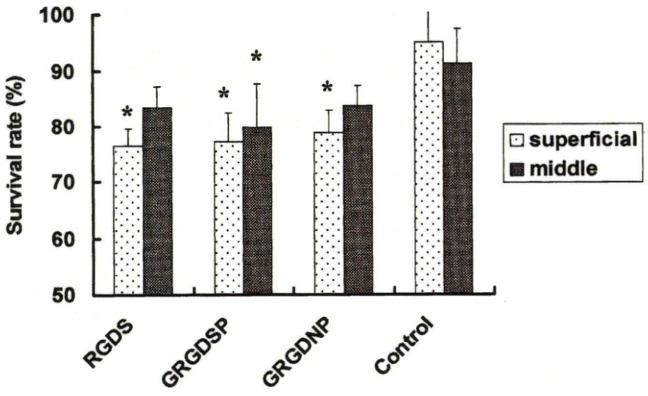

Fig. 6. Effect of RGD peptides on the viability of chondrocytes in osteochondral explants. Osteochondral explants were incubated in serum-free medium supplemented with 5 mM of RGDS, GRGDSP, and GRGDNP for 48 h. Survival rate was expressed as the percentage of live cells. In the superficial layer, the viability of chondrocytes was decreased in cartilage treated with all three peptides. In the middle layer, the viability was decreased in cartilage treated with GRGDSP. Results are shown as means and SD; $n = 4$. The value of $^*P < 0.05$ was considered significant

speculated that administering RGD peptides into an osteochondral explant would induce chondrocyte cell death by entering the cytoplasm and activating caspase-3. Furthermore, as fibronectin fragments of 29-, 50-, and 450 kDa in the synovial fluid were reported to penetrate cartilage tissue and cause cartilage damage,[15,16] RGD peptides, which are much smaller than fibronectin fragments, must be capable of penetrating cartilage tissue. Therefore, we studied the effect of RGD peptides on chondrocytes in an explant system, especially with an intact cartilage surface instead of using pieces of cartilage. As a result, significant cell death was detected. The same pathway as that in cultured chondrocytes might work in an explant system. However, we did not demonstrate direct evidence of caspase-3 activation.

Sequence dependent sensitivity

Chondrocytes showed different sensitivities to the RGD sequences. In cultured chondrocytes, GRGDSP and GRGDNP showed strong induction of cell death but RGD and RGDS did not. This difference was also observed in the caspase activity assay, where GRGDSP activated caspase-3, but RGDS did not. In contrast, RGD, RGDS, GRGDSP, and GRGDNP significantly decreased the survival rate of cultured synovial cells, in accordance with caspase-3 activation by both RGDS and GRGDSP. This suggests a sequence-dependent difference as well as a cell-type-dependent difference in the induction of cell death. The results of the present study on cultured chondrocytes were consistent with a previous report,[10] while no report has referred to the RGD-induced apoptosis of synovial cells. Further investigations are required to examine the mechanisms of sequence-dependent induction of cell death.

Significance of RGD peptide-induced cell death

The structural changes observed in osteoarthritis (OA) are complex and of multifactorial origin, including matrix degeneration and morphological changes of chondrocytes. Many reports have indicated that chondrocyte apoptosis plays an important role in the initiation and progression of OA.[17–22] Chondrocytes are known to decrease while apoptotic cells increase with age in animal models and humans.[17,22,23] Several factors

have been proposed as inducers of chondrocyte apoptosis, such as nitric oxide (NO).[24,25] Degradation of the cartilage matrix occurs during the development of OA.[18,19] These processes produce small fragments of ECM proteins. Fibronectin fragments have been found in the synovial fluid of OA patients,[26] and these fragments have been reported to cause chondrolysis of articular cartilage in bovine articular cartilage.[15,16] Fragments containing the RGD sequence must be present among them and may be one of the main inducers of apoptosis of chondrocytes. This may be an important process in the development or progression of OA and has implications for treatment in preventing the progression of OA. Morphological changes in the synovial membrane were observed in an experimental model of OA joints.[27] Apoptosis of synovial cells was also observed in OA joints.[28] An anterior cruciate ligament (ACL) transection model and meniscectomized model are commonly used as animal models for OA knees.[20,22] However, these models lead to post-traumatic secondary OA and are not ideal for studying primary OA, which is an important problem in an aged society. Our results indicate that cartilage matrix is permeable to RGD peptides and these peptides induce apoptotic cell death of chondrocytes. Administering RGD peptides into the knee joint may possibly produce a new animal model suitable for studying primary OA. Attendant synovial cell death may also enhance OA changes. On the other hand, RGDS, which preferentially induced cell death in synovial cells, might be useful for treating synovial proliferating conditions such as rheumatoid arthritis or pigmented villo-nodular synovitis.

Conclusion

In conclusion, we investigated RGD-peptide-induced apoptosis of chondrocytes and synovial cells. RGD peptides induced apoptotic cell death in cultured chondrocytes and synovial cells, as well as in chondrocytes in explants via the activation of caspase-3.

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MRIを用いた重症度評価法に基づく変形性膝関節症に対する治療法の選択

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Treatment Choice for Osteoarthritis of the Knee Joint According to Semi-automatic MRI based Assessment of Disease Severity

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Abstract

Introduction: Objective assessment of disease severity of osteoarthritis of the knee joint (OA knee) is fundamental to establish adequate treatment system. Regrettably, there is no such a reliable system. Grading system based upon X-ray findings or measurement of joint space narrowing is widely used method for this purpose but they are still far from satisfaction. Our previous study elucidated that measuring irregularity of the contour of the femoral condyle on MRI (irregularity index) using newly developed software enabled us to assess disease severity of OA objectively. Advantages of this system are expressing severity by metric variable and semi-automatic character. In the present study, we examined relationship between treatment selection and irregularity index.
Material and Methods: Sixty-one medial type OA knees that received total knee arthropaslty (TKA), arthroscopic surgery (AS), and conservative treatment (CT) were involved. Their x-ray grading, irregularity index were recorded at the time of corresponding treatment. Irregularity index of each group were compared. As for AS group, pre- and post-operative knee score employing JOA score were also examined to study relationship between irregularity index and improvement of knee score.
Results: 1) All the four parameters that represent irregularity of femoral condyle were significantly higher in TKA group than in AS group, whereas no significant difference was observed between AS

Keywords: MRI, Osteoarthritis of the knee, irregularity, severity, software
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group and CT group. 2) Negative correlation was observed between irregularity index and improvement of knee score after arthroscopic surgery.
Discussion: Although treatment selection was determined by skillful knee surgeon in this series, irregularity index could indicate adequate timing of TKA. It also served as an indicator to predict outcome of arthroscopic surgery, and could be used as to show limitation of arthroscopic surgery.
Conclusion: Our new system to assess disease severity of OA knee can serve as an index to determine treatment options.

はじめに

高齢社会となった現在，変形性膝関節症（以下膝OA）に対する適切な治療体系を確立していくことが求められている。そのためには客観的な重症度の評価法が必要となる。またこうした評価法は，治療効果や予後予測などに応用できると考えられる。

画像検査も評価法のひとつであり，レントゲン検査が汎用されている。しかし客観的な重症度の指標としての信頼度は決して高いものではない[1]。さらには，1）汎用されているレントゲンによるグレーディングシステムはさまざまな状態を呈する患者を単に4段階や5段階に分類するものであること，2）関節裂隙を測定する方法では，関節裂隙自体が1年に0.1から0.2 mm程度しか変化しないものであるため鋭敏な検査であるとはいえないこと[2]，などの問題点がある。そこで，われわれは膝OAが進行するに従い明らかとなってくるMRIで描かれる大腿骨顆部の輪郭の不整に着目し，不整度を数値化し，重症度の指標とできないかをこれまでに検討してきた。その結果，大腿骨顆部輪郭の不整度が膝OAの客観的な重症度の指標となりえることを明らかにした[3]。現在では計測するソフトウェアを改良し，半自動的に不整度の計測が可能となっている[4]。

将来的な治療体系の確立を考えた場合，大腿骨顆部輪郭の不整度を評価する方法を応用し，各症例の客観的な重症度を評価することで，個々の症例に対し適切な治療法の選択肢を提示することが可能になっていくことが期待できる。そのための端緒として，今回は不整度と実施された治療法の関係を検討し，不整度が治療法を選択する際の指標となりうるかどうかを検討してみた。

対象と方法

1）対　象

平成15年9月から平成17年4月までの間に，当施設において人工膝関節（TKA），関節鏡手術（AS），保存的治療法（CT）を受けた膝OA症例のうち，レントゲン分類のKellgren & Lawrence分類（K/L）でグレードがⅢ以上であった62膝を対象とした。

TKA群は31膝，女性25膝，男性6膝である。平均年齢は72.8歳であった。K/LグレードはⅢが4膝，Ⅳが27膝であった。AS群は18膝，女性12膝，男性6膝であった。平均年齢は69.6歳である。K/LグレードはⅢが3膝，Ⅳが15膝であった。CT群は13膝，女性10膝，男性3膝で平均年齢は70.2歳である。K/LグレードはⅢが8膝，Ⅳが5膝であった。

2）不整度の計側

不整度を計測する手順であるが，第一にMRIの元の画像データ（DICOM data）をコンピュータに取り込み，白黒画像化し，大腿骨内側化の輪郭のみを抽出する。その後専用に開発されたソフトウェアにより，抽出された輪郭に対し，自動的に輪郭の厚みの平均（Average Thickness of Subchondral plate: ATS），厚みのばらつき（Standard Deviation of the thickness of the Subchondral plate: SDS），厚みの2乗の平均（Average Squared Thickness of the Subchondral plate: ASTS），輪郭の上縁の長さと下縁の長さの比（Ratio of

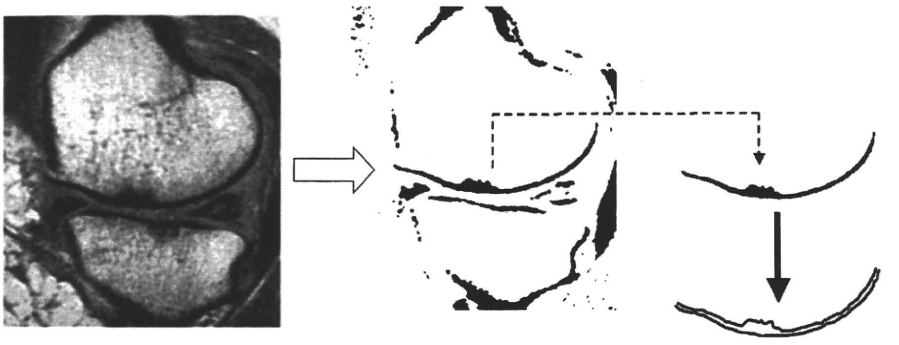

図1　MRIによる大腿骨内側顆の輪郭の評価法
MRI画像のデータ（DICOM）をコンピュータの取り込み，白黒画像へと変換する（⇨）。その後大腿骨内側顆の輪郭のみを抽出し（⇢），抽出された輪郭の上縁と下縁をトレースしたのち，ピクセル毎に輪郭の幅（上縁と下縁の間の距離）と上縁と下縁の長さの比が計測される。

表1　各治療群の不整度

	TKA (N=31)	AS (N=18)	CT (N=13)
ATS	8.2±2.6	* 5.8±1.2	5.4±2.5
		N.S.	
RUL	1.21±0.12	* 1.114±0.07	1.09±0.11
		N.S.	
ASTS	96.7±70.1	* 40.0±16.3	60.9±60.1
		N.S.	
SDS	4.1±1.5	* 2.7±0.8	2.1±1.4
		N.S.	

the length of Upper surface and the Lower surface of the subchondral plate: RUL）が計算される[4]（**図1**）。

3）不整度と治療法の関係

検討1としてTKA，AS，CT群の不整度の計測と比較を施行した。また検討2として関節鏡手術を受けた群の術後成績と術前の不整度の関係を調べた。なお，AS群の術後成績はJOAスコアと4段階の満足度調査で行った。4段階とは，大変満足である，満足である，どちらともいえない，不満である，である。

4）統計学的検討にはMann-WhitneyのU検定，相関係数を用いた。

結　　果

検討1

各治療群の不整度を表1に示した。ATS，SDS，ASTS，RULの4つの不整度をあらわすいずれのパラメータもTKA群とAS群間では有意差があった。しかし，AS群とCT群間では有意差がなかった（**表1**）。各群への治療の振り分けは，患者の要望，社会的背景，身体所見な

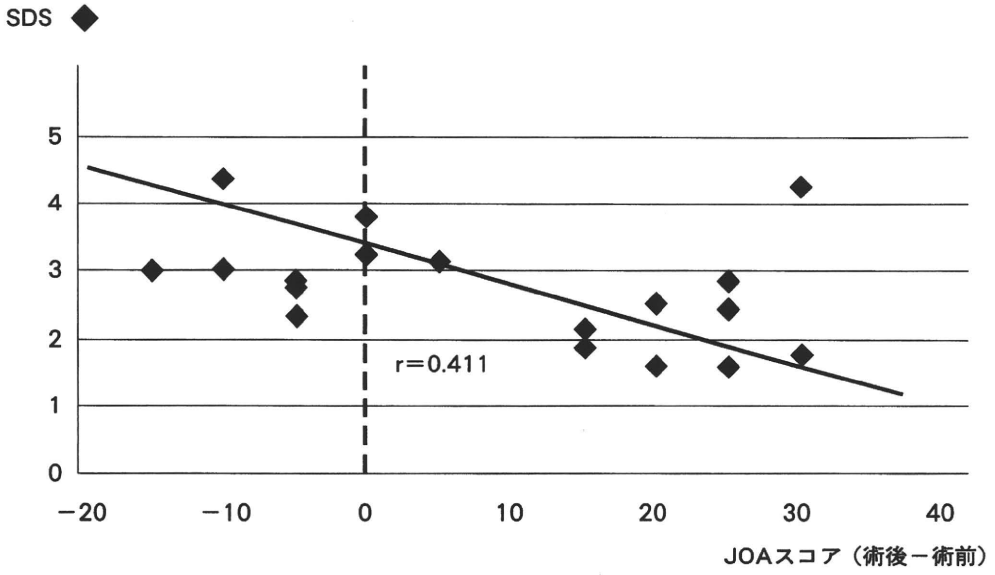

図2　不整度（SDS）とJOAスコアの変化
AS群を縦軸にSDSとし横軸にJOAスコアの変化（術後―術前）としてプロットすると，負の相関があることがわかった。

どの各種要素を勘案した上で経験ある整形外科医が決定していたわけだが，結果として不整度はTKA群においては明らかに高くなっていた。すなわち不整度はTKAの適応を決める指標となり得ると言えそうである。

検討2

検討2では関節鏡手術症例の不整度と術後成績の関係を調べた。術後観察期間は1年9ヵ月から3年8ヵ月で，平均で2年9ヵ月であった。

全症例のJOAスコアは術前平均63.1点が術後平均71.9点に改善していた。

JOAスコアの改善点と不整度の4つのパラメータとの関係を調べたところSDSにのみ弱いながら負の相関のあることがわかった（**図2**）。すなわち不整度の高かった症例ほど術後成績の改善が見られないことを意味する。

ついでSDSの値で2群に分けてみると，満足度の調査でも不整度の少ない群において満足度の高いことがわかった（**図3**）。

図4に代表的な4つの症例を提示するが，左の2膝は改善のよかった症例であり，右の2膝は改善の得られなかった症例である（**図4**）。

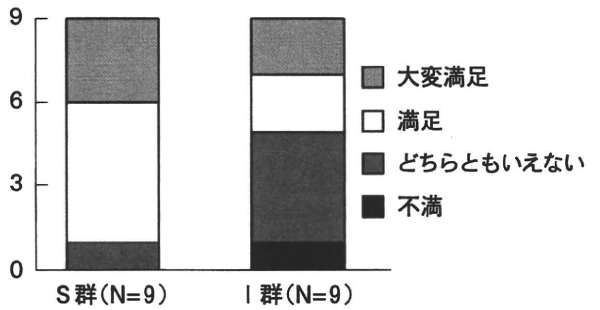

図3　不整度と満足度
SDSの値により症例を半分に分け，低値の群（S群），高値の群（I群）とするとS群において9症例中，3症例が「大変満足」，5症例が「満足」と回答しており満足度の高いことがわかった。一方I群では満足度が低かった。

いずれの症例も内側型膝OAであり，レントゲン所見上は症例1の関節症性変化が少ないことがわかるが，症例2，3は同程度の変化である。また4症例いずれも内側コンパートメントの矢状断像MRIにおいては大腿骨内側顆の前方に同程度の骨棘の形成が見られる。症例1のみは内側半月板が描出されているが，症例2，3，4では描出されてはいない。また，今回計測した大腿骨内側顆の不整度であるが，症例1では不整度が軽度であることは肉眼的に判断できるが，