Increased Levels of Interleukin-6 in Synovial Lavage Fluid From Patients With Mandibular Condyle Fractures: Correlation With Magnetic Resonance Evidence of Joint Effusion

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Purpose: The aim of the present study was to investigate the relation between magnetic resonance (MR) evidence of joint effusion and concentrations of proinflammatory cytokines, including interleukin (IL)-1β and IL-6, in washed-out synovial fluid samples obtained from patients with mandibular condyle fractures.

Patients and Methods: Twenty-five joints in 23 patients with mandibular condyle fractures were examined. Computed tomography was used to determine the position of the fracture and MR examination was performed in all cases. Twenty-five joints underwent temporomandibular joint (TMJ) irrigation before surgical treatment for the fractures. The detection rates and concentrations of the tested cytokines were determined, and their relations to evidence of joint effusion and positions of the condylar fractures were analyzed.

Results: Six TMJ fractures were found in the head, 10 in the upper neck, 4 in the lower neck, and 5 in the subcondyle. MR evidence of joint effusion was observed in 17 of 25 TMJs (68.0%). The detection rate and concentration of IL-6 were significantly higher in patients with MR evidence of joint effusion and those with high condylar fractures. Moreover, there was a correlation between joint effusion grade and IL-6 concentration.

Conclusions: The present findings showed a correlation between MR evidence of joint effusion and concentration of IL-6 in washed-out synovial fluid samples collected from patients with mandibular condyle fractures. These results may provide support for arthrocentesis as a reasonable treatment modality for high condylar fractures.

J Oral Maxillofac Surg 71:1050-1058, 2013

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Conflict of Interest Disclosures: None of the authors reported any disclosures.

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0278-2391/13/00106-7$36.00/0

http://dx.doi.org/10.1016/j.joms.2013.01.021

Conservative treatment options for mandibular condyle fractures consist of intermaxillary fixation (IMF) and rehabilitation, including jaw motion exercises,[1,2] which have not changed since 1947.[3] In contrast, an international consensus for the treatment of those fractures has not been reached regarding the choice of surgical reduction over nonsurgical modalities.[4,5]

Even when a favorable outcome is achieved by conservative treatment with IMF, functional recovery requires a lengthy and sometimes distressful rehabilitation. From experimental findings, Ellis[6] suggested that IMF delays the recovery of the mandibular range of motion after orthognathic surgery. Thus, it is considered important to establish a shorter and less painful treatment protocol for patients with condylar fractures. Joint irrigation with saline solution (arthrocentesis) has been used therapeutically for patients with pain and dysfunction of the temporomandibular joint (TMJ),[7] with outcomes of irrigation into the superior joint compartment found to be satisfactory for various types of TMJ diseases.[8-11] In addition, intra-articular corticosteroid injections have been applied successfully as treatment for TMJ pain and dysfunction,[12] and Kondoh et al[13] reported that arthrocentesis for mandibular condyle fractures was effective.

Mandibular condyle fractures frequently cause injury to soft tissues of the TMJ. Some studies have used arthroscopy to show that intra-articular damage generally occurs when the mandible is fractured.[14,15] Furthermore, magnetic resonance (MR) evidence of joint effusion, which is depicted on T2-weighted images as an increased signal in the joint compartment, is frequently observed after a mandibular condyle fracture.[16] Although MR evidence of joint effusion represents inflammatory changes, its clinical and biological significance in the TMJ after such fracture remains unclear. Segami et al[17] reported that synovial fluid from TMJs with internal derangement and osteoarthrosis with joint effusion contained higher concentrations of total proteins and the proinflammatory cytokines interleukin (IL)-6 and IL-8 compared with samples from TMJs without joint effusion.

The purpose of the present study was to investigate the relations between MR evidence of joint effusion and concentrations of proinflammatory cytokines in washed-out synovial fluid (SF) samples obtained from patients with mandibular condyle fractures. Such MR evidence was examined to determine the inflammatory changes related to extravasation of protein molecules. In addition, SF analyses of joint lavage (JL) fluid samples collected from the superior joint space of the TMJ in patients with mandibular condyle fractures were performed, and the levels of inflammatory mediators, including total protein and IL-1β and IL-6, were measured as a biological investigation of the effectiveness of arthrocentesis for a fractured TMJ with joint effusion.

Patients and Methods

PATIENTS AND CLINICAL ASSESSMENT

This prospective study was approved by the ethics committee of Kyushu Dental College. The authors examined 25 joints in 23 patients (16 male, 7 female; average age, 42.5 years; range, 19 to 80 years) with mandibular condyle fractures who underwent arthrocentesis for therapeutic purposes. In all cases, the TMJs were evaluated on MR images before treatment (Table 1).

Radiographic examinations included a panoramic transcranial view (open and closed mouth) and computed tomography to determine the position of the mandibular fracture. Computed tomograms were acquired using a Toshiba X Vision RE (Toshiba Co Ltd, Tokyo, Japan). Helical scanning was performed with a slice thickness of 1 to 2 mm and the following parameters: 120 kVp, 220 ms, and table speed of 2 mm/second. The field of view was 18 cm (512 × 512 matrix). The types of condylar fracture in relation to the mandible were classified according to the classification of MacLennan,[18] with some modifications.

Type I: fracture with no displacement
Type II: fracture deviation
Type III: fracture displacement with the condyle remaining in the fossa
Type IV: fracture deviation with dislocation
Type V: fracture displacement with dislocation

Three TMJs were classified as type I, 4 as type II, 5 as type III, 3 as type IV, and 10 as type V (Fig 1). The positions of the fractures were divided into 4 areas—head, upper neck, lower neck, and subcondyle—with head fractures considered to occur at the junction of the head and neck, essentially an intracapsular fracture. Fractures above the level of the depth of the sigmoid notch and below the head were classified as neck fractures and were divided further into the upper and lower neck areas. Those below the level of the most inferior point of the sigmoid notch were classified as subcondylar (Fig 2). The authors classified the position of 6 TMJ fractures in the head, 10 in the upper neck, 4 in the lower neck, and 5 in the subcondyle. The types and condylar positions of the fractures are listed in Table 1. The etiologies of the fractures were falls in 14 patients (60.9%), assault in 6 (26.1%), sports injury in 1 (4.3%), and traffic accidents in 2 (8.7%). In addition, 7 patients had an additional mandibular body fracture. The time from injury to the first visit ranged from 0 to 21 days (average, 7 days), whereas that from injury to MR examination ranged from 3 to 24 days (average, 11.3 days). In all patients, the MR examination was performed for diagnostic purposes before beginning any treatment procedure, after obtaining

Table 1. CLINICAL DATA

Patient Number	Age (yr)	Side	Gender	Condylar Fracture		Joint Effusion	SF Analysis	
				Type	Position		IL-6 (pg/mL)	IL-1β (pg/mL)
1	64	L	F	V	head	○	104.1	0.9
2	35	L	M	V	upper neck	○	16.1	ND
3	31	L	M	III	head	○	44.3	ND
4	23	L	M	V	upper neck	○	180.9	1.4
5	19	L	M	I	subcondyle		ND	ND
6	24	L	F	I	head		ND	10.2
7	71	R	F	III	subcondyle		ND	ND
8	25	L	M	I	subcondyle		ND	ND
9	40	L	F	V	upper neck	○	13.3	ND
10	27	L	M	V	lower neck	○	ND	ND
11	52	L	M	IV	upper neck	○	3.4	7.1
12	63	R	M	V	head	○	1,129.9	0.6
13	62	R	M	III	upper neck	○	2.8	ND
14	19	L	F	II	upper neck	○	179.8	0.2
15	19	R	F	III	upper neck	○	190.0	5.5
16	80	R	F	V	upper neck	○	13.9	ND
17	26	L	M	II	lower neck		ND	0.96
18	47	L	F	V	lower neck	○	178.1	ND
19	21	L	M	II	subcondyle		ND	1.1
20	58	R	M	IV	upper neck	○	172.9	ND
21	72	R	M	V	head	○	363.5	16.9
22	72	L	M	V	head	○	1,416.4	5.3
23	23	R	F	II	subcondyle		ND	2.5
24	40	L	M	IV	upper neck	○	0.3	ND
25	55	L	M	III	lower neck		ND	1.2

Abbreviations: F, female; IL, interleukin; L, left; M, male; ND, not determined; R, right; SF, synovial fluid.

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informed consent, and using procedures approved by the ethics committee of Kyushu Dental College. At this institution, treatment for these fractures is dependent on the position and type. In cases with fractures in the upper region of the condyle (n = 14), a closed reduction was performed, which included IMF for 5 days. In cases with fractures in the lower region of the condyle or in those with a severely displaced condylar fracture (n = 9), the authors used a retromandibular approach or endoscopy-assisted open reduction and internal fixation to perform an open reduction with dual mini-titanium plate fixation. In those 9 cases, the SF sample was collected from the JL before performing the open reduction.

MR image examinations were performed in all cases using a 1.5-T MR imaging scanner (Visert, Toshiba Co Ltd) with a bilateral 3-inch dual-surface. Sagittal closed- and open-mouth spin-echo T1-weighted images and sagittal and coronal closed-mouth fast spin-echo proton- and T2-weighted images were used for evaluation. The parameters for the T1-weighted spin-echo sequence used were a repetition time of 1,050 ms, an echo time of 15 ms, a 160 × 288 matrix, a 15-cm field of view, and a slice thickness of 3 mm. Fast spin-echo images used a repetition time of 3,500 ms and an echo time of 108 ms for T2-weighted images. MR evidence of joint effusion was evaluated as previously described.[19] Briefly, on T2-weighted images, joint effusion was identified as an area of high signal intensity in the region of the superior or inferior joint space. On proton- and T1-weighted images, the signal intensity in these areas was not increased. The joint was considered positive for joint effusion when more than a single line of high intensity was evident in at least 2 consecutive sagittal sections; otherwise, the joint was considered negative. Evaluations of MR evidence of joint effusion and the types and positions of mandibular condyle fractures were performed at least 2 times at different time points by 2 of the authors (S.N. and T.T.) who were blinded to the patients' names and clinical information. When there was disagreement, the final assessment was reached by consensus. The degree of joint effusion was determined as described by Segami et al,[20] and that in the superior compartment was divided into 4 grades: 0, no area of high signal intensity; 1, a line or spot of high intensity along the articular surface; 2, a band of high intensity; and 3, collection with pooling in the compartment.

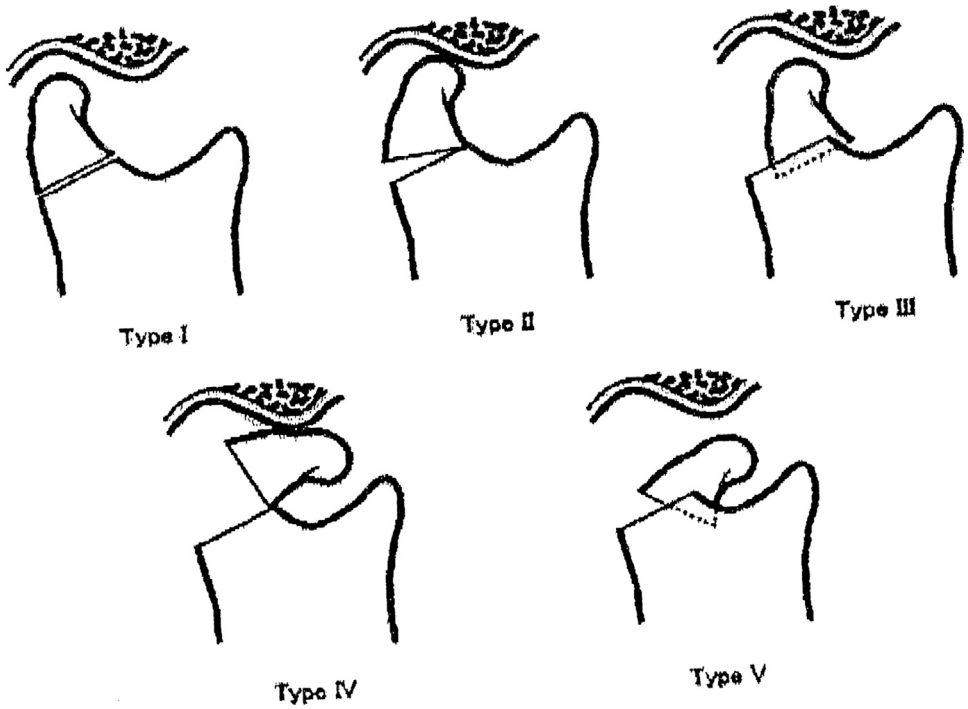

FIGURE 1. Classification of mandibular condyle fracture types. Type I, fracture with no displacement; type II, fracture deviation; type III, fracture displacement; type IV, fracture deviation with dislocation; type V, fracture displacement with dislocation.

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JL FLUID SAMPLE PREPARATION

All SF samples were collected by the same author (T.T.), who is a TMJ specialist. SF samples of the JL obtained from the superior joint space were collected from the patients and control subjects after a pumping procedure by washing the joint with physiologic saline, as previously described. Seven asymptomatic healthy volunteers (5 male, 2 female; mean age, 35.2 years) comprised the control group. They had no clinical signs or symptoms involving the TMJ or disc derangement.

Briefly, after local anesthesia, 2 mL of physiologic saline solution was injected into the superior joint space, and then the mouth was opened and closed to mix the saline solution with the SF. The mixture of SF and saline was then aspirated, and the procedure was repeated for a total of 10 times. Thereafter, the JL sample was collected, centrifuged at 800*g* for 5 minutes to remove cells, and stored at −80°C until being assayed. The recovery of JL samples ranged from 60% to 120%, with a mean recovery of 100%. JL samples containing blood resulting from active bleeding caused by the sampling procedure were excluded from the study. For all patients, informed consent was obtained before treatment using a procedure approved by the ethics committee of Kyushu Dental College.

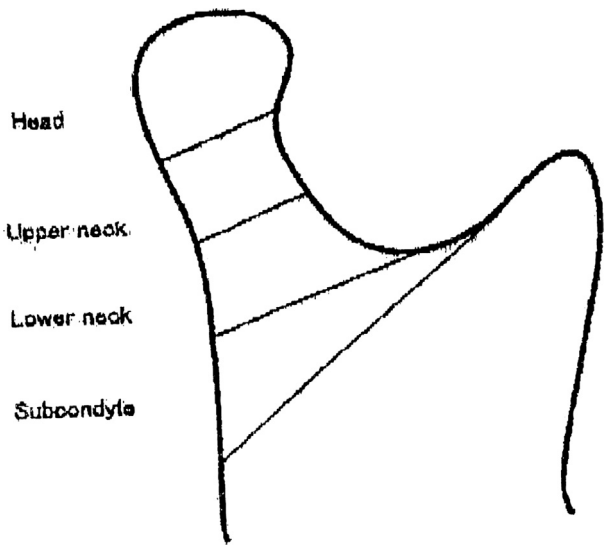

FIGURE 2. Classification of position of mandibular condyle fractures.

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MEASUREMENTS OF IL-1B AND IL-6

Concentrations of the proinflammatory cytokines IL-1β and IL-6 were determined using an enzyme-linked immunosorbent assay kit (Quantikine; R&D Systems, Inc, Minneapolis, MN) according to the manufacturer's instructions. The detection limit for each cytokine was 1 pg/mL. The same surgeon (S.N.) measured the concentrations of IL-1β and IL-6.

Table 2. POSITIONS OF MANDIBULAR CONDYLE FRACTURES AND JOINT EFFUSION

	With JE	Without JE
Head (n = 6)	5	1
Upper neck (n = 10)	10	0
Lower neck (n = 4)	2	2
Subcondyle (n = 5)	0	5

Abbreviation: JE, joint effusion.

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STATISTICAL ANALYSIS

Differences in concentrations of IL-1β and IL-6 were analyzed using the Mann-Whitney *U* test, with $P < .05$ considered statistically significant. The Spearman correlation coefficient was used to compare joint effusion grade with the concentration of IL-1β and IL-6.

Results

MR evidence of joint effusion was observed in 17 of 25 TMJs (68.0% of all cases). That evidence was observed in all patients with high condylar fractures, except for patient 6. Results of the enzyme-linked immunosorbent assay showed that IL-1β protein was detected in 13 TMJs (52.0%), whereas expression of IL-6 protein was observed in 16 TMJs (64.0%). In contrast, neither IL-1β nor IL-6 was detected in any of the JL samples from the control group.

Furthermore, IL-6 was detected in all fractured TMJs with joint effusion except for patient 10, whereas no IL-6 expression was found in fractured TMJs without joint effusion (Table 1). Detection of IL-1β was not as typical as that of IL-6. MR evidence of joint effusion was observed in nearly all patients with head and upper neck fractures (Table 2). The concentration of IL-6 was significantly higher in TMJs with joint effusion compared with those without effusion ($P < .05$; Fig 3A). However, there was no correlation between concentration of IL-1β and the presence of joint effusion ($P > .05$; Fig 3B). For the fracture position, high condylar fractures showed a significantly higher concentration of IL-6 than low condylar fractures ($P < .05$; Fig 4). Moreover, there was a correlation between joint effusion grade and IL-6 concentration ($P < .01$; Fig 5A), whereas there was no correlation between joint effusion grade and IL-1β concentration ($P > .05$; Fig 5B).

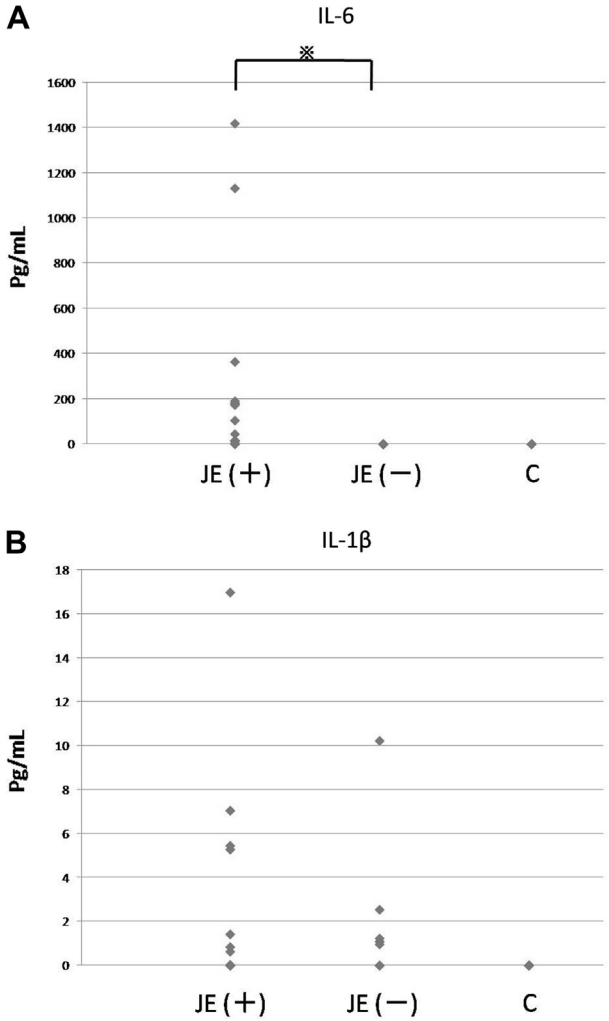

FIGURE 3. Concentrations of the cytokines *A*, interleukin-6 and *B*, interleukin-1β in cases with and without joint effusion. Horizontal bars indicate the mean value. ※$P < .05$, Mann-Whitney *U* test. C, control group; IL, interleukin; JE (−), no joint effusion; JE (+), with joint effusion.

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Discussion

Because of the extended T2 period of free water, most body fluids are easily detected by T2-weighted MR imaging, in which fluids have an intense signal compared with solid tissue.[21,22] The vast majority of orthopedic studies of other joints, such as the knees and hips, have shown that joint effusion is caused by trauma, internal derangement, rheumatic disorders, hemophilia, and infections.[23] Specifically, joint effusion seems to be related to hemarthrosis and inflammatory changes accompanying soft tissue injuries and arthralgia.[23-26] In addition, some studies have noted that MR evidence of joint effusion is frequently observed in TMJs of patients with internal derangement and osteoarthritis (OA) of the TMJ.[19,27,28] Although MR evidence of joint effusion can be observed in joint compartments of the TMJ after a condylar fracture, little is known about its frequency and significance. Sullivan et al[29] reported evidence of joint effusion by MR after condylar fractures, although they did not

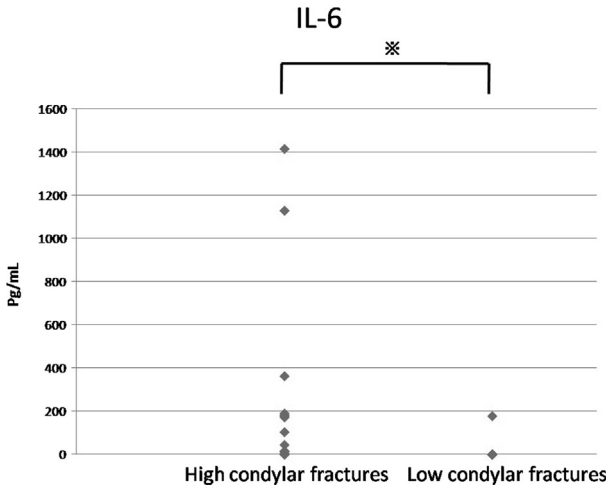

FIGURE 4. Concentrations of interleukin-6 and mandibular condyle fracture positions. High condylar fractures, head and upper neck fractures; low condylar fractures, lower neck and subcondylar fractures. ※$P < .05$, Mann-Whitney U test. IL, interleukin.

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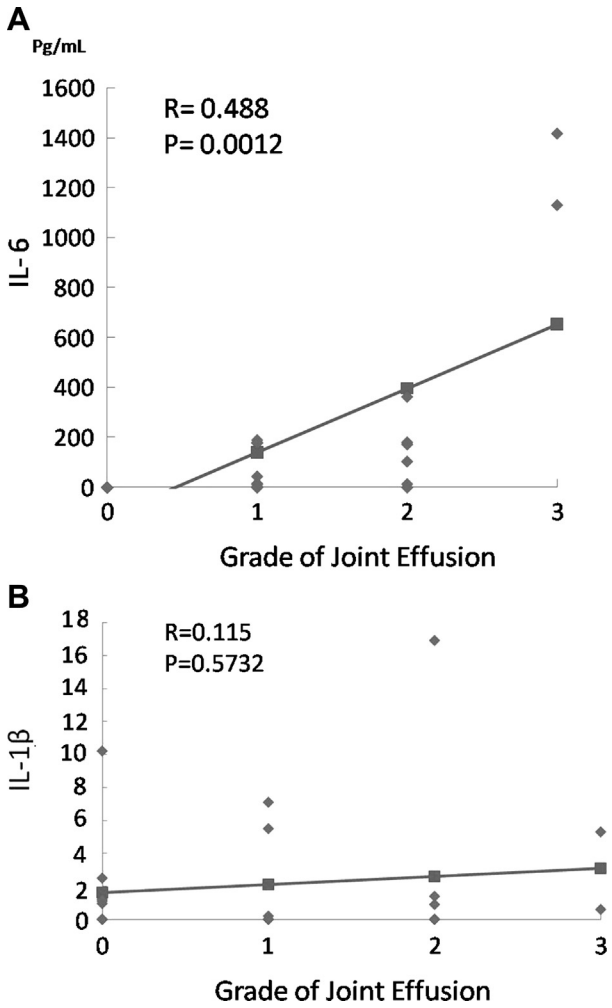

FIGURE 5. Distribution of grades of joint effusion and concentrations of *A*, interleukin-6 and *B*, interleukin-1β. Significant correlations are indicated by means values obtained in a Spearman correlation coefficient by rank test. IL, interleukin.

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investigate the frequency of effusion or its correlation with fracture type and position. Schellhas[30] also found evidence of joint effusion by MR in patients with complicated acceleration-deceleration injuries. However, because the time from injury to imaging differed significantly among cases (2 days to 24 months), it was not clear whether MR evidence of joint effusion was directly related to the soft tissue injuries or the subsequent clinical course. Because all the present patients were referred to the authors' department from other hospitals, the periods from injury to imaging were significantly different.

Intra- and extracapsular condylar fractures are associated with hemoarthrosis.[31] Using arthroscopy, Goss and Bosanquest[14] found intra-articular damage, including hemarthrosis, and shedding of the disc and joint surfaces in most examined TMJs. Jones and Van Sickels[15] also reported the existence of hemarthrosis in 12 of 15 joints by arthroscopy and found that the amount of blood seen in the joint decreased as the delay from injury to treatment increased. These findings suggest that hemarthrosis is the major pathology occurring in the TMJ after a condylar fracture. Because joint effusion is closely related to hemarthrosis after joint injury,[26] the present evidence of joint effusion in TMJs frequently observed by MR imaging after condylar fractures probably represented hemarthrosis occurring in the joint.

Acute bleeding and hematomas are displayed as high-intensity signals on T2-weighted images.[21,32] Thus, MR evidence of joint effusion in the TMJ after a mandibular condyle fracture may represent acute bleeding. However, this is unlikely for the following reasons. Most hematomas present with bright signal intensity and inhomogeneous signals on T1- and proton-weighted images.[32] However, all the present joints showed homogenous signals on T1- and proton-weighted images, and the signal intensity on those images was not increased in any of the joints. These findings suggest that MR evidence of joint effusion after a condylar fracture does not merely reflect acute bleeding in the joint compartment.

In the present study, the mean time from injury to MR imaging examination was 11.3 days (range, 3 to 24 days). Experimentally induced hemarthrosis resolves spontaneously within the first week after injury[33]; however, Goss and Bosanquest[14] reported that hemarthrosis spontaneously resolved within 5 to 7 days, with some residual hemosiderin visible in some joints for a longer period. Jones and Van Sickels[15] also noted that the amount of blood in the joint decreased with an increased delay from injury to treatment, suggesting that hemarthrosis might subside

within a relatively short period. Conversely, it is interesting to note that even at 10 days after injury evidence, joint effusion remained in 68.0% of the cases. Thus, evidence of joint effusion on MR images after a condylar fracture may be related to not only hemarthrosis but also joint inflammation, such as synovitis.

Previous studies have clearly shown that hemarthrosis leads to synovial hypertrophy and acute inflammation,[33,34] and it has been shown that hyperemia and thickening persist. Inflammatory cells in synovial tissue also persist for as long as 2 weeks after injury.[34] Therefore, MR evidence of joint effusion that appears in joint compartments after a condylar fracture also represents inflammatory changes and subsequent extravasation of protein molecules because of increased permeability. The ultimate study to clarify whether evidence of joint effusion after a condylar fracture reflects the presence of hemarthrosis or joint inflammation, such as synovitis, would include MR image examinations combined with arthroscopic evaluations of hemarthrosis and synovitis in the same patients.

In the present study, all TMJs with dislocation examined after a condylar fracture showed MR evidence of joint effusion, with joint effusion observed in the upper and lower joint compartments in 40% of the present patients. In addition, evidence of joint effusion appeared more frequently in high compared with low condylar fractures. Provided that MR evidence of joint effusion is related to hemarthrosis or inflammatory changes occurring in the TMJ, these findings suggest that MR evidence of joint effusion after a condylar fracture may reflect the severity of the impact on the TMJ components. Interestingly, none of the TMJs in cases with unilateral condylar fractures showed evidence of effusion on the nonfractured side. In contrast, using arthroscopic findings, Goss and Bosanquest[14] reported that TMJs showed greater damage on the nonfractured side compared with the fractured side and explained that condylar neck fractures would mechanically decrease the degree of direct intra-articular trauma by decompression. One possible explanation for not finding MR evidence of joint effusion in contralateral TMJs is that mechanical damage to the nonfractured side is not adequate to cause joint effusion. Interestingly, subcondylar fractures showed lower levels of effusion in the present patients, which may be explained by Goss and Bosanquest's concept that mechanical stress is decompressed in such fractures, all of which were without dislocation, whereas it is directly compressed in upper condylar fractures, most of which also involved dislocation in the present cohort.

Among the advantages of MR imaging as a diagnostic modality are the lack of ionizing radiation and noninvasive characteristics.[35] Although arthroscopy is a potent modality for investigating intra-articular damage after condylar fractures, it is indicated only for patients undergoing surgical treatment. Although preliminary, the present study found that MR evidence of joint effusion in the TMJ may serve as a marker of severe intra-articular damage. Nevertheless, further studies with large numbers of joints and shorter periods until MR image examination will be necessary to explore the clinical, biological, and biochemical significance of MR evidence of joint effusion after mandibular condyle fractures.

Previous studies have found increased concentrations of IL-1β, tumor necrosis factor-α, and IL-6 in SF from TMJs with degenerative changes.[36-41] Those cytokines may induce the release of proteinases, stimulate the expression of matrix-degrading enzymes and inflammatory mediators, and promote the degradation of cartilage and bone and inflammation in the joint. IL-6 levels have been shown to be significantly increased in SF and serum obtained from patients with rheumatoid arthritis.[42,43] Moreover, Kubota et al[44] found that IL-6 was elevated in SF obtained from patients with TMJ and localized OA. Lee et al[45] also reported higher concentrations of IL-6 in SF from patients with temporomandibular disease compared with a healthy volunteer group.

In joints, this cytokine is produced by synovial cells, monocytes, macrophages, and fibroblasts.[41,44,46] IL-6 also plays a major role in mediating inflammatory and immune responses initiated by infection and injury. Previous reports have shown that IL-6 is a key proinflammatory factor in arthritis, and studies of animal models have established that this cytokine plays a main role in the pathogenesis of arthritis.[47] IL-6 knockout mice are protected against adjuvant-induced polyarthritis, whereas the effects of IL-6 on osteoclasts, osteoblasts, and bone remodeling are complex and vary among diseases.[48]

Donald et al[49] reported experimental and clinical research on post-traumatic OA (PTOA). PTOA is closely related to the energy delivered to the joint at the time of injury and the resulting severity of articular surface damage.[50,51] They also reported that P188 alone or in combination with growth factors may have the potential to prevent the development of PTOA. P188 affects stress-related p38 signaling, apoptosis-related glycogen synthase kinase 3, and inflammation-related IL-6 signaling.[49,52] Lower levels of IL-6 may prevent the development of PTOA. Clinically, arthrocentesis may have an effect on preventing the development of PTOA by decreasing the levels of IL-6 in the joint cavity.

In the present study, IL-6 was detected only in cases of high condylar fractures with MR evidence of joint effusion. However, IL-1β was detected at the same rate as IL-6 in the present patients. IL-1β appears earlier than

IL-6. Because the time from injury to the collection of SF samples was about 2 weeks in the present cases, the authors presume that the concentration of IL-6 was higher than that of IL-1β in those samples. In addition, the significant correlation between joint effusion grade and concentration of IL-6 is an important finding. Thus, it is likely that IL-6 can be detected in cases of high condylar fractures with MR evidence of joint effusion.

Segami et al[20] reported that joint effusion was closely correlated with the severity of synovitis detected using an arthroscopic technique. Moreover, Sandler et al[41] noted that the presence of IL-6 was correlated with the degree of acute synovitis, whereas IL-1β and tumor necrosis factor-α were not found in significant levels within the superior joint space. Decreased IL-6 levels in patients taking nonsteroidal anti-inflammatory drugs have been shown in in vitro[53] and in vivo[54] experimental studies, which, as noted in the latter study, may be related to the general anti-inflammatory effect of the drugs or nonsteroidal anti-inflammatory drugs exerting a direct effect on IL-6 production.

Kondoh et al[13] found that intra-articular irrigation and corticosteroid injection resulted in quick recovery of jaw function and shorter duration of distress in patients with unilateral fresh mandibular condyle fractures. The authors speculate that arthrocentesis may cause lower levels of proinflammatory cytokines that lead to synovitis.

In conclusion, the present results suggest that arthrocentesis may be a potent treatment modality for patients with high condylar fractures, because it decreases the level of IL-6, which seems to be responsible for synovitis in the TMJ after a condylar fracture. To obtain additional evidence, further studies regarding IL-6 concentrations and evaluations of synovitis are currently being performed.

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