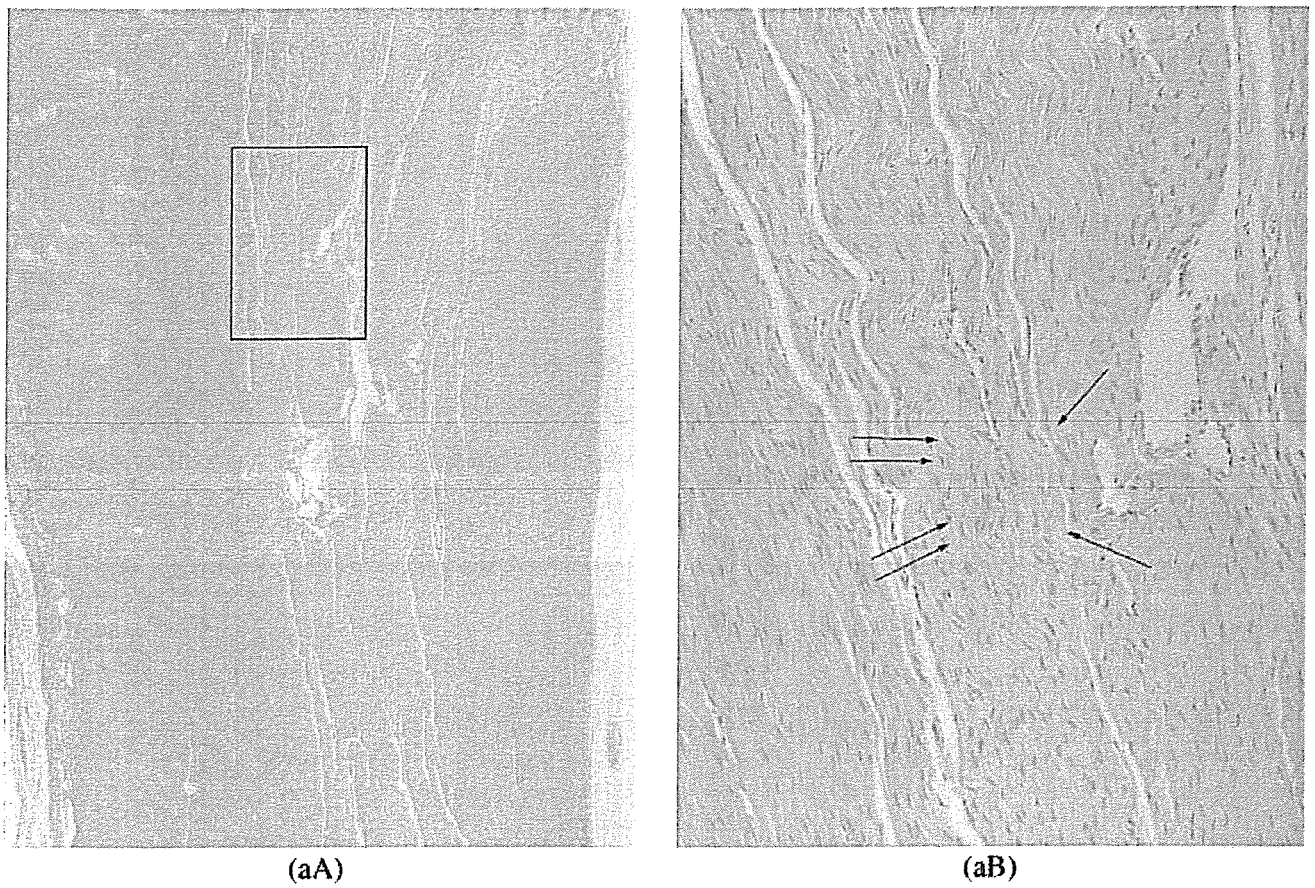
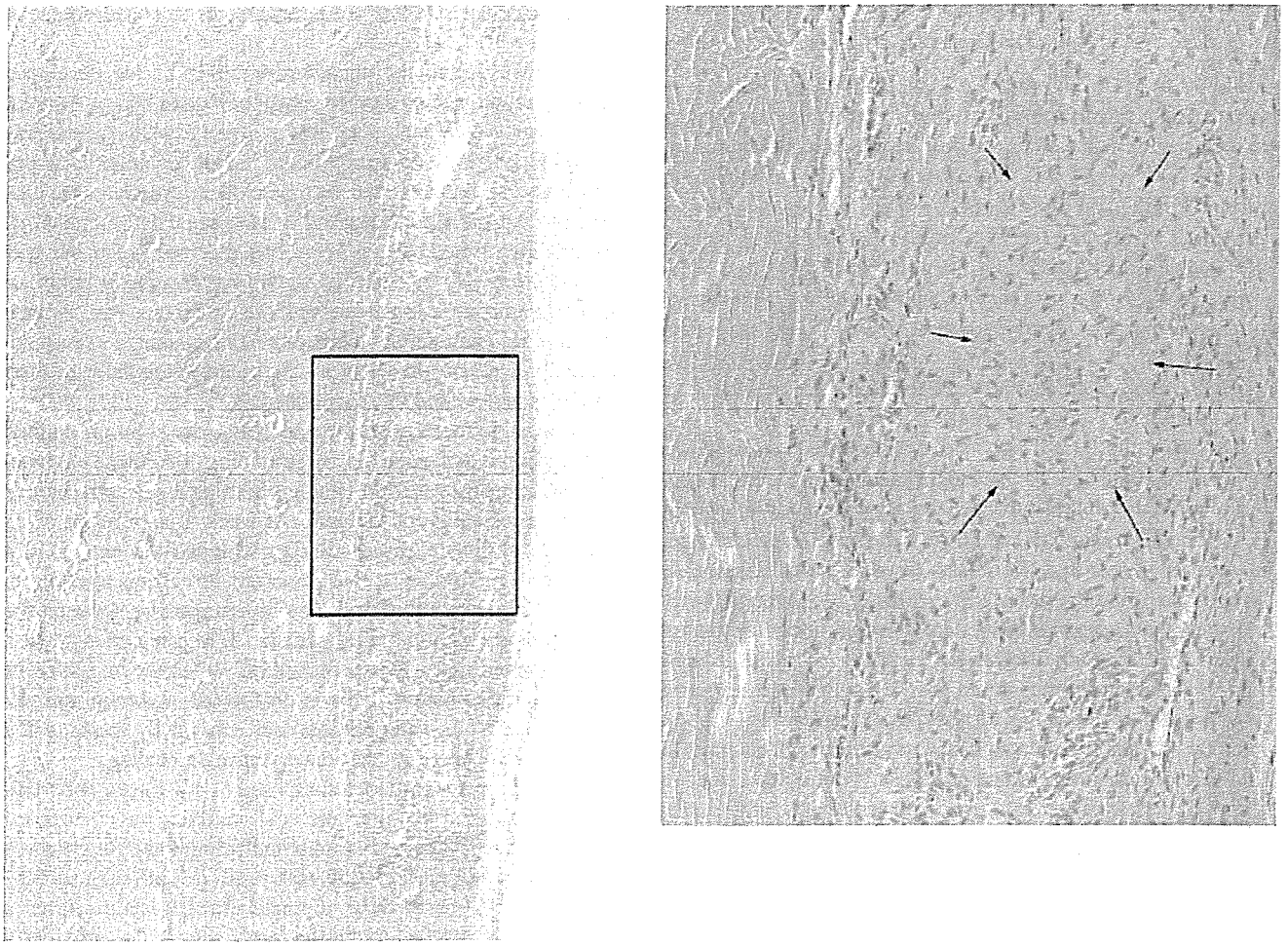


Figure 3. (a) Histological findings in the alginate-treated group. (A) View of the entire injured tendon. The left side shows the unlacerated portion of the tendon (×10). (B) Higher magnification of the inset in (A) (×40). Arrows indicate longitudinal, smooth remodeling of the collagen fibers. (b) Histological findings in the control group. (A) View of the entire injured tendon. The left side shows the unlacerated portion of the tendon (×10). (B) Higher magnification of the inset in (A) (×40). Arrows indicate that a random pattern of fibers was still evident.

ulated at the knee. The skin and muscles were removed, leaving the flexor digitorum tendon intact at the posterior aspect of the leg. The tendon was dissected free from its bony origin, and a pair of forceps was attached to its proximal end. The leg was observed from the medial side in front of a white screen bearing radial lines representing a protractor; lines were drawn every 10 degrees from horizontal to 360 degrees. The first metatarsophalangeal joint capsule was exposed and the head of the first metatarsal bone was positioned at the center of the protractor. The limb was placed in a vertical position with its proximal tibia immobilized by a clamp while the mid and anterior parts of the foot were left free and positioned horizontally. The posterior part of the foot, including the calcaneus, was held in another clamp. The flexion angle of the first toe was measured to the nearest 5 degrees when the proximal end of the tendon was pulled with 400 g force (measured by a spring-type scale) (Figure 1). We positioned a camera at a fixed distance from the screen and photographed the limb in the resting position and when weight was applied to the tendon. When the photographs were developed, the flexion range of motion was determined as the difference between the resting position and the flexed position. The observer (K.S.) was blinded to the treatment each animal received. The flexion ratio was calculated by dividing the flexion angle of the surgically treated side by the angle of the nonsurgically treated side and was expressed in percentage. An unpaired t test was used to evaluate the differences between the treated and control groups at 4 weeks.

Histological Evaluation

Tendon healing, peritendinous adhesion, and the state of alginate solution remaining locally were evaluated by observing the appearance of the repaired site with the naked eye at postoperative week 4. A longitudinal section of the repaired site was stained with hematoxylin and eosin and observed microscopically to determine the amount of scar formation and to evaluate the remodeling of collagen fibers.



(bA) (bB)

Figure 3. (continued)

RESULTS

At 4 weeks postoperatively, the wound site had healed well in all animals. No evidence of rupture, faulty union, local inflammation, or systemic complications was observed.

Mechanical Evaluation

Flexion ratio was significantly greater in the alginate-treated group (81.5 ± 17.4; SE = 4.35) than in the control group (64.4 ± 17.0; SE = 4.26) at 4 weeks postoperatively (p = 0.009) (Table I).

Histological Evaluation

Macroscopic Appearance of the Lesion Site. Repair of the lacerated sites appeared complete at week 4 in both groups. The amount of scar formation at the repaired tendon was greater in the control group than in the alginate-treated group [Figure 2(a,b)]. However, this was difficult to quantify. In the alginate-treated group, the repaired tendon was surrounded by a transparent membrane [Figure 2(b)], which was thought to be a mixture of alginate paste and the original synovial fluid. In all alginate-treated rabbits, a yellowish paste was observed within the intact sheath at the ankle at week 4, which was thought to be undissolved alginate paste [Figure 2(c)], and the tendons healed, with good appearance in terms of physical properties and luster [Figure 2(d)]. In all animals in the control group, union was attained but the original luster was lost.

Histology. In both groups, fibroblasts and collagenous tissue had proliferated at the repaired site. However, longitudinal well-oriented tenocytes, indicating smooth remodeling of the collagen fibers, were observed in all toes in the alginate-treated group [Figure 3(a)], whereas poorly oriented cells and a random pattern of fibers were still seen in the control group [Figure 3(b)].

DISCUSSION

In the last decade, scientific evidence supported the theory that the extrinsic mechanism might merely be an inflammatory response to tendon injury rather than being essential to the process of tendon repair.[13] In an effort to minimize adhesion after tendon repair, biochemical materials such as monomolecular cellulose filter tubes,[1] polyethylene tubes,[2] and silastic sheaths[3] have been tested as mechanical barriers around the repair site, but no satisfactory approach has been established. All these materials failed because they stimulated a severe inflammatory response or prevented nutrient diffusion to the healing tendon, leading to tendon necrosis.

Currently, both intrinsic and extrinsic mechanisms are believed to contribute to the tendon healing process.[6] Tenocytes within the tendon and epitenon play an important role in the intrinsic mechanism, while in the extrinsic mechanism, inflammatory cells and fibroblasts from the overlying sheath and periphery are the main participants.[13,14] Although synovial sheath cells move into the tendon core soon after tendon injury,[5] there is a time lag in the initiation of intrinsic healing.[6] It is therefore considered that if an intrinsic response could be stimulated at the early stage of tendon healing, the outcome of tendon repair would be preferable with regard to reducing peritendinous adhesion. Based on this idea, a wide range of substances, including fibrin sealant,[11] 5-fluorouracil,[12] sodium hyaluronate,[15] aprotinin,[16] and TGF-β1 neutralizing antibody,[17] have been experimentally applied to the tendon repair, with the aim of reducing extrinsic healing and stimulating the intrinsic mechanism. However, problems such as high cost of raw materials, potential side effects, and limited bioavailability have prevented widespread clinical use of these agents.[17]

We have accordingly focused our attention on alginate, a natural biodegradable material, rather than on the development of synthetic pharmacologic substances.

Recently, alginate has been used as a wound dressing material and as a food additive on account of its high viscosity and good biocompatibility.[7] It is also used extensively in cell encapsulation and tissue engineering because of its easy gelation, good biocompatibility, and low toxicity.[7,18] The best results have been obtained with alginate microcapsules in the field of allo- and xenogenic islet transplantation.[8] In cell encapsulation, alginate gel that is crosslinked with covalent bonds is generally applied. However, this has a hard consistency, making it unsuitable for application as a coatable or injectable tendon adhesion barrier gel. To create alginate with adequate handling properties, we developed a technique involving very high concentrations of sodium alginate without using the crosslinking method. As high-molecular-weight alginate chains in this formulation adopt very coiled configurations in solution, we considered that this results in alginate occupying a large volume for its mass and acting as a sieve for molecules and cells passing through the solution. Ideally, such a configuration would allow permeation of molecules such as oxygen, glucose, insulin, and other nutrients of small molecular size that are necessary for cells and organs to survive.

We investigated the antiadhesive effect of the developed alginate solution using a rabbit model of tendon injury. At week 4, the most critical time after tendon surgery, tendon repair was not inhibited, and statistically better tendon excursion was obtained in the alginate-treated group. Macroscopically, alginate remained in the sheath at week 4. Histologically, longitudinal remodeling of the collagen fibers was observed in the alginate-treated group. No evidence of tendon rupture, faulty union, or local inflammation was observed. This suggests that alginate solution has no inhibitory effect on tendon healing and does not cause foreign body reaction, as confirmed in the fields of food additives and wound dressing materials.[7]

A possible mechanism by which alginate solution inhibits peritendinous adhesions is by providing a suitable environment for intrinsic tendon healing, both as a selective barrier and as a cell delivery medium. At week 4, as a result of its adhesive ability, alginate solution wrapped the tendon in a manner very similar to that observed in cell encapsulation. Instilled alginate solution works by interposing between the lacerated tendon and the injured sheath as a selective barrier, thereby avoiding early scar formation. When the migration of extrinsic inflammatory cells is obstructed, epitenon and endotenon cells from the tendon itself can easily move to the lacerated site, thereby facilitating intrinsic healing.

Alginate is a copolymer composed of 1,4-linked β-D mannuronic acid and α-L-gluronic acid residues, has a carboxyl base (—coo—) attached to its branch chain, and functions as a polyanion polymer that attracts positive ions such as Na^+ and Ca^{2+}.[7] Consequently, alginate attracts water, forms a hydrogel, and swells around the repair site. It also provides a suitable environment for diffusion and transportation of certain nutrients.[18]

Both the low cost of production and bioabsorbability of alginate may render it very useful in the clinical setting. Because all species of brown seaweed contain the source molecule algin, alginate is abundant enough to be used commercially.[7] Alginate is largely produced in the food industry as a stabilizer in ice cream and as a thickener in fruit drinks.[7] Although usually hydrolyzed by alginate lyase in brown seaweed, alginate takes longer to be hydrolyzed in the human body because humans lack the appropriate hydrolyzing enzyme.[7] Alginate therefore remains for several weeks at the repair site, a great advantage considering the time frame of tendon healing. Hyaluronate, which is also a biodegradable mucopolysaccharide and well known as one of the main components of synovial fluid, has also been used experimentally to prevent peritendinous adhesion.[15] However, in contrast to alginate, hyaluronate is rapidly broken down in the human body by hyaluronidase and disappears within 72 h.[19]

In summary, the results of the present study suggest that alginate solution is an effective material for inhibition of peritendinous adhesion, and that its application represents a promising approach for treating tendon injury. Although alginate solution showed a favorable antiadhesive effect in our

rabbit tendon model, further studies are required to determine suitable concentration and viscosity in clinical use.

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Clin Rheumatol
DOI 10.1007/s10067-006-0318-y

ORIGINAL ARTICLE

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Radiographic study of joint destruction patterns in the rheumatoid elbow

Received: 7 January 2006 / Revised: 1 April 2006 / Accepted: 3 April 2006

Abstract Knowledge of the pattern of joint destruction is important for planning the therapeutic approach to rheumatoid arthritis (RA) of the elbow. Accordingly, we carried out a large-scale radiographic study with the objective of elucidating the joint destruction pattern in rheumatoid elbows. From 2001 through 2003, we examined and took plain X-rays of both elbows of 193 RA patients (i.e., 386 elbows), consisting of 18 men and 175 women, with a mean age of 57.0 years. Radiographic images of the elbow joints were used to classify the degree of bone loss in various zones on the elbow joint surface into four grades of severity, and joint destruction was compared between the left and right elbows. In addition, correlation in the extent of bone loss between each of the zones of the same elbow and differences in the extent of bone loss were analyzed statistically. The results showed direct correlations for destruction of the elbow joint surface among the zones for the left and right elbow joints and in the same elbow joint. However, more severe destruction was observed on the radial side of the humeral trochlea, and it was surmised that destruction of the elbow joint must begin at that site and gradually spread mediolaterally. In addition, in the same elbow joint, the correlation in the degree of bone loss between the trochlea of humerus and the trochlear notch was especially strong, indicating that the bone destruction at both sites represented mirror lesions. We conclude that when performing radiographic diagnosis of the joint damage in the rheumatoid elbow, knowledge of this pattern of joint destruction will be useful for assessing whether there is joint destruction in the initial stage and for deciding the therapeutic approach.

Keywords Elbow joint · Radiography · Rheumatoid arthritis

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Introduction

The elbow joint is a common site for the development of rheumatoid arthritis (RA), and it is one of the most important joints in the upper limb as it controls the reach of the hand [1–4]. For this reason, disorders of the elbow joint can seriously interfere with activities of daily living (ADL) of RA patients. In general, when arthropathy is mild, therapy consists of conservative treatments such as drug administration and/or intraarticular injection of steroid. In severe disease, surgical treatments such as synovectomy and artificial elbow joint replacement may be performed [1–4]. For treatment selection and planning, it is very important for the physician to have a good understanding of the pattern of destruction that has occurred in the RA elbow joint. However, it is unfortunate that to date very few reports of analysis of the pattern of bone destruction in RA elbow joints have been published.

We therefore carried out a large-scale radiographic study with the objective of elucidating the pattern of RA elbow joint bone destruction.

Subjects

From 2001 to 2003, we examined plain X-rays of both elbow joints of 233 patients who satisfied the ARA diagnostic criteria. Forty of these patients were excluded from the present study due to previous synovectomy or

artificial elbow joint replacement (33 patients) or because the X-rays were unreadable (seven patients). The remaining 193 RA patients, i.e., 386 elbows, were the subjects of this study. They consisted of 18 men and 175 women, with an age range of 23~84 years (mean 57.0 years). History of drug administration, including steroids, and duration of RA were unclear.

Methods

Radiographic classification of the severity of RA was performed on the basis of plain X-ray anteroposterior images and lateral images of the bilateral elbow joints that were obtained for each patient at the time of final examination. X-rays were taken with the patient in a sitting position. Frontal views were obtained with the elbow joint extended and the forearm in the supine position, while lateral views were obtained with the elbow joint flexed at 90° and the forearm in the intermediate position. The frontal images were divided into three zones: the capitulum of the humerus (zone A), the radial side of the humeral trochlea (zone B), and the ulnar side of the humeral trochlea (zone C). The extent of destruction of the joint surface was determined for each of these zones. In addition, from the lateral view, the extent of joint surface destruction was determined for the olecranon (zone D).

Extent of joint destruction was assessed by reference to a template of the normal elbow joint that had been prepared in advance. The ratings used were grade 0, no bone loss; grade 1, less than 3 mm of bone loss from the joint surface; grade 2, bone loss of 3 to less than 6 mm; and grade 3, bone loss of 6 or more mm (Figs. 1 and 2).

We investigated the extent of bone destruction observed in each of the joint zones, and also investigated whether there was any correlation in destruction among the zones. In practice, we first investigated the correlation in the extent of bone loss in the same zone in both elbows of the same patient, and then compared joint destruction in the left and right elbows. In addition, the correlation in the extent of bone loss among each zone of the same elbow and differences in the extent of bone loss were analyzed statistically.

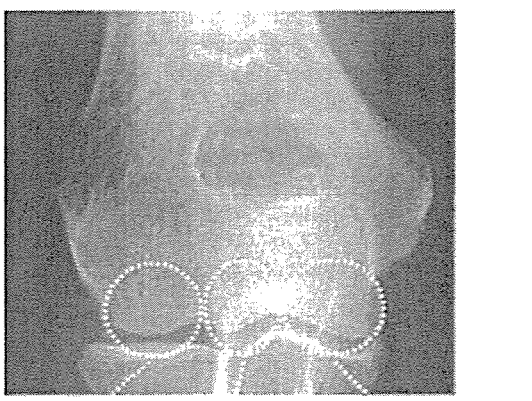

Fig. 1 Radiographic classification (*zones A, B,* and *C*)

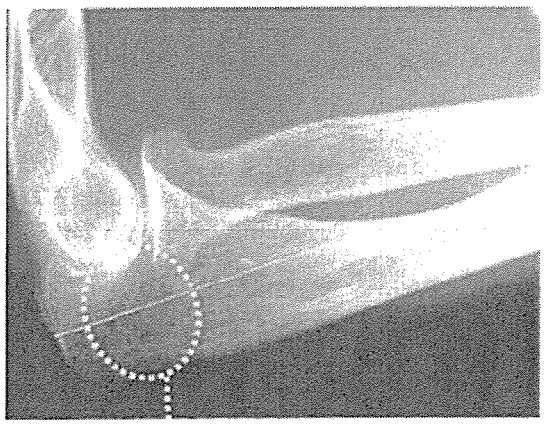

Fig. 2 Radiographic classification (*zone D*)

Spearman's ranked correlation coefficients were used for statistical analyses of correlations, while one-way analysis of variance (ANOVA) and Fisher's least significant difference (LSD) test were used to analyze differences in extent of bone loss.

Results

The extent of bone loss in each zone of the joint as seen on frontal X-ray images was as follows: zone A, 26.2% grade 0, 62.1% grade 1, 8.8% grade 2, and 2.8% grade 3; zone B, 26.2% grade 0, 37.0% grade 1, 26.9% grade 2, and 9.8% grade 3; and zone C, 26.9% grade 0, 62.1% grade 1, 2.6% grade 2, and 8.3% grade 3. The extent of bone loss was therefore similar in zone A and zone C, whereas zone B exhibited a lower percentage rated as grade 2 and a higher percentage rated as grade 3 compared with the other two zones. The extent of bone loss seen on lateral X-ray images (zone D) was grade 0 in 27.2%, grade 1 in 61.1%, grade 2 in 8.3%, and grade 3 in 3.4% (Table 1).

A significant correlation was found for the extent of bone loss in the same zone between the left and right elbows, and correlation was found for bilateral elbow joint destruction (zone A r=0.833, p<0.001; zone B r=0.804, p<0.001; zone C r=0.881, p<0.001; and zone D r=0.887, p<0.001).

In addition, statistically significant correlations were also found for the extent of bone loss among zones in the same elbow (r=0.789~0.951, p<0.001) (Fig. 3). A particularly strong correlation was demonstrated between zone C and zone D (r=0.951, p<0.001).

On the other hand, the extent of bone loss was significantly greater in zone B compared with zone A and zone C (p<0.05), indicating that joint surface

Table 1 Radiographic classification of severity of joint destruction in the elbow (n=193)

Grade	Zone A		Zone B		Zone C		Zone D	
	R/L	Total(%)	R/L	Total(%)	R/L	Total(%)	R/L	Total(%)
0	50/51	26.2	49/52	26.2	51/53	26.9	51/54	27.2
1	123/117	62.2	73/70	37.1	120/120	62.2	117/119	61.1
2	14/20	8.8	54/50	26.9	7/3	2.6	16/16	8.3
3	6/5	2.8	17/21	9.8	15/17	8.3	9/4	3.4
Total	193/193	100	193/193	100	193/193	100	193/193	100

destruction was more advanced in the central part of distal humerus articular surface than at other sites (Fig. 4).

In addition, bone destruction of the humeral trochlea that extended to the olecranon fossa, i.e., a so-called Y-shaped

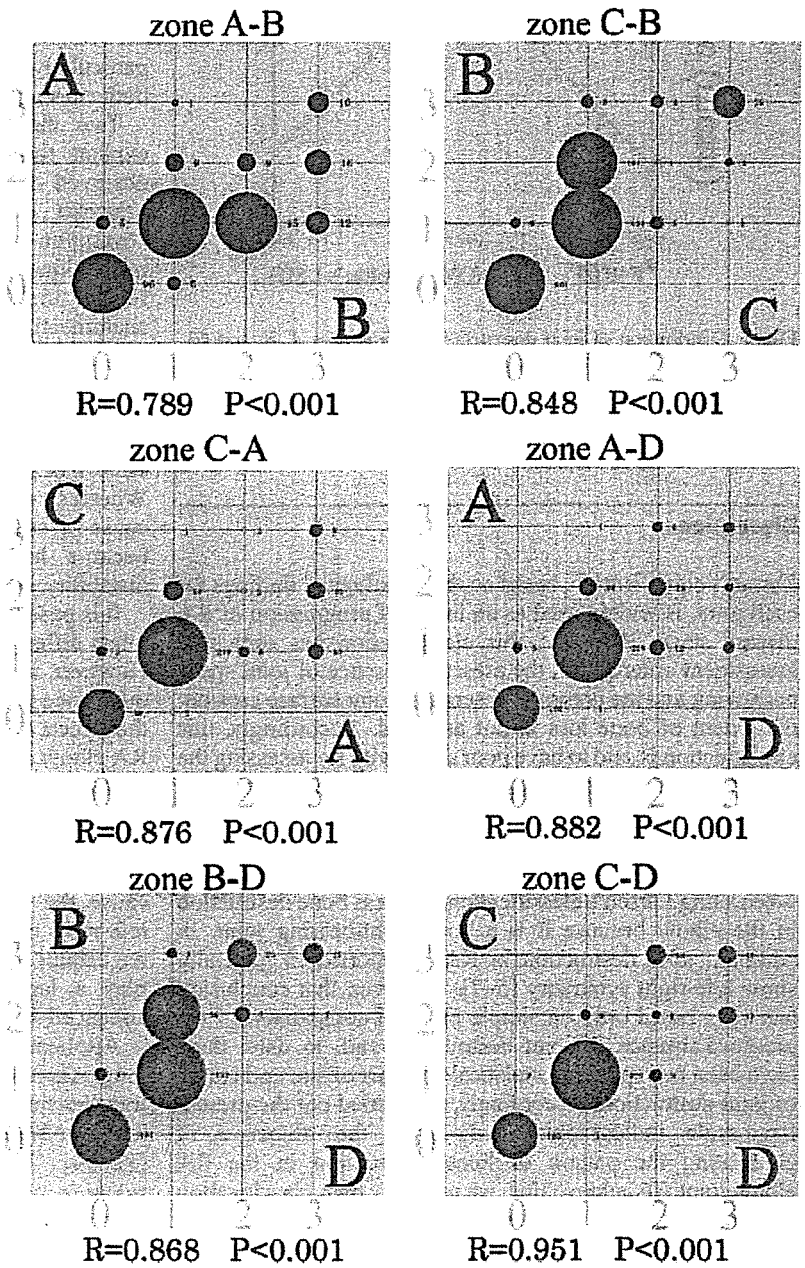

Fig. 3 Correlation of joint destruction among *zones A, B, C,* and *D* (386 joints)

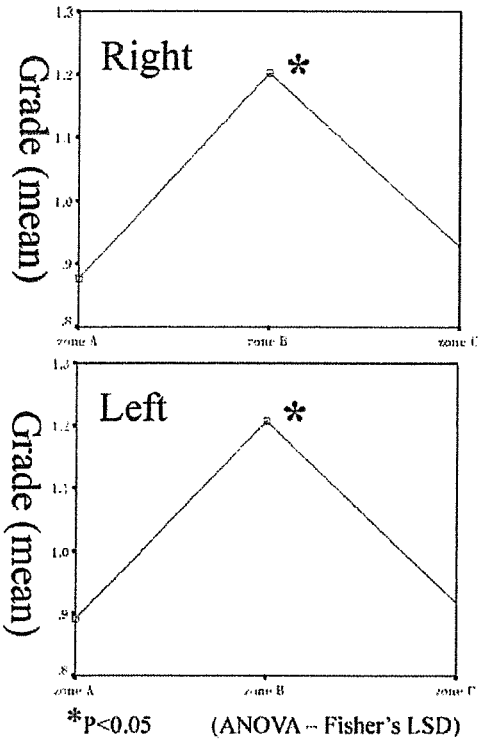

Fig. 4 Distribution of joint destruction grade (*zones A*, *B*, and *C*)

deformity, was observed in six of the patients, although this was bilateral in only two patients.

Discussion

Larsen's classification, based on the radiological findings for each joint, is widely used as an index of progression of RA disease stage. However, this classification has only two assessment criteria, i.e., the presence/absence of joint space narrowing and the presence/absence of joint surface erosion; the extent of bone loss is not assessed. Accordingly, this classification is said to have poor sensitivity for assessing the extent of joint destruction [5–7]. Lehtinen et al. [7] reported that joint space narrowing in the RA elbow differs from that in weight-bearing joints in that it occurs only subsequent to erosive destruction. They also stated that caution is necessary when using Larsen's classification to assess bone destruction in the elbow because it is a nonweight-bearing joint. In addition, joint destruction in RA is reported to generally show left–right symmetry [5–7]. However, that conclusion has been based only on simple bilateral comparison of the presence/absence of joint destruction, and, to date, there have been no reports of statistical analysis of site and extent of joint destruction. Accordingly, we carried out the present large-scale radiographic study with the objective of elucidating the pattern of bone destruction in the RA elbow joint. To achieve this, we used our own classification system to assess the extent of bone loss in various zones on the elbow joint surface, and joint destruction was compared between the left and right elbows. We then performed statistical analyses to determine whether there were any correlations in the extent of bone loss among each of the zones in the bilateral elbows and in the same elbow.

Our patients showed positive correlations among each of the zones for the extent of bone loss in the same elbow joint, and positive correlations were also found for the extent of joint surface bone loss in the same zones in the bilateral elbows. On the other hand, when we investigated the extent of bone loss in each zone in the same joint, we found it to be significantly greater on the radial side of the humeral trochlea compared with the ulnar side of the trochlea and the capitulum. We therefore surmised that the joint destruction must begin at the radial side of the humeral trochlea and gradually spread mediolaterally. In addition, in the same elbow joint, the correlation in the degree of bone loss between the ulnar side of the trochlea and the olecranon was particularly strong, indicating that the bone destruction at both sites represented symmetrical lesions.

Two theories have been proposed in an attempt to explain the underlying mechanism of the destruction observed in upper limb joints with RA. In the first, the principal cause is considered to be destruction and absorption of cartilage and bone as a result of the actions of cytokines released from the synovial tissue [8, 9]. The second theory holds that the major effects arise from anatomical and/or mechanical factors [10]. Ochi et al. [11] reported that even in the same joint the mechanism of destruction varies widely depending on the disease type. That is, they found that in the type involving damage to the smaller joints, the main bone destruction consisted of erosion of the joint surface due to proliferation of synovitis. Whereas with the mutilating type of arthritis, the main cause of bone destruction was crushing of bone that had become highly osteoporotic because of severe joint instability due to joint laxity.

It is possible that the level of stress applied to the elbow joints differs between the dominant and nondominant arm. However, in the present study, we found no clear left–right difference in the extent of joint destruction, suggesting that the effects of mechanical factors on bone destruction in the RA elbow are slight. Even so, consideration must be given to the fact that most of the patients in our present series were at an earlier stage of the disease, showing a milder degree of joint destruction. Conversely, however, some patients with severe joint destruction, such as is likely to cause the so-called Y-shaped deformity, exhibited clear left–right differences in the extent of damage. Therefore, we cannot rule out the possibility that mechanical factors play a larger role than immunological factors in the advanced stages of joint destruction.

Application of axial compression in the direction of the long axis of the forearm reportedly results in almost equal transmission of the force to the radial joint and the ulnar joint, or slightly greater transmission to the radial joint [12–14]. The surface of the radial side of the humeral trochlea becomes the varus–valgus pivot point of the elbow [15], and for this reason it is possible that when joint laxity occurs due to synovitis, forces are concen-

trated in that area and this leads to the progression of joint destruction.

Our present results indicated the possibility that joint destruction in the RA elbow begins on the radial side of the humeral trochlea and gradually spreads mediolaterally. If we accept the validity of this pattern of destruction of the elbow joint, then when analyzing X-rays taken in the early stage of RA elbow joint damage, it should be possible to focus on the radial side of the humeral trochlea and determine whether joint destruction had already begun. In addition, if bone destruction on the radial side of the trochlea were mild, we would be able to conclude that the joint destruction was at an early stage and that a minimally invasive therapy such as synovectomy was indicated.

The progression of joint destruction can be considered influenced by various factors, such as medication (including NSAIDs, DMARDs, and steroids), disease duration, and progression of joint deformation due to aging or osteoporosis [16–19]. A limitation of the present study was that we were unable to discuss the possible effects of drug treatments, disease duration, and aging in our patient series. However, this is the first report of a statistical analysis of the pattern of joint destruction in the rheumatoid elbow, and we think that our findings will make a significant contribution to decision making regarding therapeutic approaches to RA of the elbow.

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