Corticosteroid treatment induces chondrocyte apoptosis in an experimental arthritis model and in chondrocyte cultures

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Abstract

Object

In order to examine the mechanisms involved in steroid-induced arthropathy after intra-articular corticosteroid injection, a histological examination was performed in vivo using severe combined immunodeficiency (SCID) mice that were implanted with human articular cartilage into the back (SCID/hu model). In addition, the effect of corticosteroids on chondrocyte apoptosis was evaluated in vitro using cultured human chondrocytes.

Method

Human articular cartilage was obtained during knee surgery and implanted subcutaneously into the backs of SCID mice. One month later, weekly injections of corticosteroid (hydrocortisone acetate: 1mg/0.2ml, triamcinolone acetonide: 0.2mg/0.2ml, dexamethasone acetate: 0.1mg/0.2ml) in the subcutaneous cavity around the grafted cartilage in SCID mice were initiated. After six weeks of treatment, the grafted cartilage pieces were removed from the SCID mice and examined histologically. Chondrocyte apoptosis after corticosteroid treatment was also investigated using cultured human chondrocytes.

Result

In the corticosteroid treated, grafted articular cartilage, apoptotic chondrocytes were apparent in the superficial and middle layers of cartilage. But a reduced intensity of Safranin O staining was not remarkable. In the cultured chondrocytes, apoptotic changes were also observed after corticosteroid treatment.

Conclusion

Corticosteroid treatment induces chondrocyte apoptosis and it may be important to understand the steroid-induced arthropathy.

Key words

Corticosteroid, apoptosis, chondrocyte, SCID/hu model.

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Introduction
Corticosteroid injections are frequently used to achieve local anti-inflammatory activity (1). And it is well known that repeated intra-articular corticosteroid therapy interferes with cartilage metabolism and may lead to rapid destruction of the joint. In one of the most famous textbook of rheumatology, corticosteroid arthropathy was described. It was printed that abuse of intra-articular injections may result in a Charcot-like arthropathy (2). Corticosteroids exert powerful anti-inflammatory effects through inhibition of the arachidonic acid cascade. However, the pharmacological mechanism of corticosteroid-induced arthropathy remains unclear (3-5).

Recently, corticosteroids were reported to induce the apoptosis of lymphocytes, eosinophils, bone and cartilage of growth plate (6-8). These results suggest that similar corticosteroid-induced apoptosis may occur in articular cartilage. Chondrocyte apoptosis has already been reported to play important roles in cartilage degradation and in the pathogenesis of joint cartilage degeneration (9-13). However, if corticosteroids are able to induce chondrocyte apoptosis, this may explain, at least in part, the pharmacological mechanism of steroid-induced arthropathy. Therefore, in the present study, we investigated the histological changes in human articular cartilage after repeated corticosteroid injections using the severe combined immunodeficiency (SCID) mouse in which human articular cartilage had been grafted (SCID/hu model) (14-16). In this model, the implanted human articular cartilage maintained the characteristics of in vivo human cartilage, and enabled histological examination of the grafted cartilage after corticosteroid treatment without any confounding mechanical influences. In addition we examined the induction of chondrocyte apoptosis in vitro.

Material and methods
Preliminary examination to invest the effect of corticosteroid on the rabbit articular cartilage
Weekly corticosteroids (hydrocortisone acetate: 1mg/0.2ml, Banyu Co. Tokyo Japan, triamcinolone acetonide: 0.2mg/0.2ml Sankyo Co. Tokyo, Japan. dexamethasone acetate: 0.1mg/0.2ml, Banyu Co. Tokyo Japan) injections were performed to the rabbit (Japanese white rabbit 2 months old: Japan Clea Inc., Tokyo, Japan) knee for six weeks. Each corticosteroid was injected to 3 rabbit in the right knee, and the left knee was used for control. Three days after the final injection, the articular cartilage were extirpated and used for the histological investigation of chondrocyte apoptosis and matrix degradation.

Transplantation of human articular cartilage to the back of the SCID mouse (SCID/hu model)
The SCID/hu model, which we have previously described (14-16), was used for the study of corticosteroid treatment. Briefly, male SCID mice (CB.17/lcr; Japan Clea Inc., Tokyo, Japan), 6-7 weeks old and bred under specific pathogen-free conditions at our university animal center, were used. Articular cartilage, collected at the time of total knee arthroplasty, was used for implantation. Undamaged cartilage samples from non-weight bearing region such as an inter-condylar part were collected from 7 OA patients (ages were 57-68 years: average was 63.1 years). These cartilage were usually wasted in the process of surgery. Parts of these samples were examined histologically and confirmed to be intact. All patients gave informed consent to be tissue donors in this study. The size of the donor articular cartilage was adjusted to a block of 5 mm across prior to its subcutaneous implantation into SCID mice. The mice were anesthetized with dimethylether, according to the guidelines established by our university’s animal ethics committee, and the human articular cartilage blocks were grafted subcutaneously into their backs. All surgical procedures were performed under sterile conditions and the result of culture test was negative.

Corticosteroid injection protocol
The initial injection of corticosteroid was administered one month post-
Implantation, after the graft had taken in the SCID mice. Six cartilage pieces were acquired from 1 donor and a total of 40 mice were used in this experiment. Pairs of corticosteroid-treated and control mice were implanted with articular cartilage from the same patient. Weekly corticosteroid (hydrocortisone acetate: 1mg/0.2ml: 1.4 x 10^{-3}M; triamcinolone acetonide: 0.2mg/0.2ml: 2.5 x 10^{-3} M; dexamethasone acetate: 0.1mg/0.2ml: 1.1 x 10^{-3}M) injections were given in the subcutaneous cavity around the grafted tissue of 30 SCID mice (hydrocortisone acetate: 10 mice: triamcinolone acetonide: 10 mice: dexamethasone acetate: 10 mice). Triamcinolone acetonide (TA) is clinically used for intra-articular injection in humans (1). Generally, the optimal dose of TA for treatment of arthritic disease has been considered to be 10-40 mg/1-4 ml: 2.5 x 10^{-3}M per single injection in human. As a control, phosphate-buffered saline (PBS) alone was injected in the same manner into the other 10 SCID mice. The weekly injections were performed for six weeks. Three days after the final injection, the implanted tissues were removed from mice in each treatment group, and used for the histological investigation of chondrocyte apoptosis and matrix degradation.

Histological examination of implanted cartilage after corticosteroid treatment

Upon removal, the implanted articular cartilage pieces were fixed in 4% neutral-buffered formaldehyde. Embedded in paraffin wax, each tissue block was cut into 6 µm sections and applied to slides. Sections were dewaxed, hydrated and stained with hematoxylin and eosin (HE) and Safranin O (SO) at room temperature. Sections were also analyzed using terminal deoxynucleotidyl transferase (TdT)-mediated dUTP nick end labeling (TUNEL) staining, as previously described (16). Briefly, the tissue sections were dewaxed and hydrated, and the proteins were stripped off using 20 µg/ml of proteinase K (Boehringer-Mannheim Co. Ltd. Germany) at room temperature prior to TUNEL staining. Endogenous peroxidase was quenched with 3% H_{2}O_{2}. The specimens were then labeled in TdT buffer (30 mM Tris-HCl, pH 7.4, 140 mM sodium cacodylate, 1 mM cobalt chloride) and reacted with biotinylated dUTP dissolved in TdT buffer. Finally, the samples were stained with 3,3’-diaminobenzidine. For electron microscopy, the samples were prepared as previously described (16). Briefly, they were fixed in 0.1 M cacodylated buffer containing 3% glutaraldehyde at 4˚C for 1 hour. After subsequent incubation in 1% OsO_{4} for 1 hour, the samples were dehydrated and embedded in epon, then sliced to obtain ultra-thin sections 1000Å thick. The sections were then stained with uranyl acetate and lead citrate for electron microscopic observation.

**Human articular chondrocytes culture**

Articular cartilages were removed from 7 OA patients. Part of each sample was engrafted into a SCID mouse, and the remaining portion of the sample was used for in vitro experiments. Articular chondrocytes were isolated as reported previously (17), and analyses were performed on each sample 3 times. Briefly, cartilage specimens were minced under sterile conditions and treated with 1 mg/ml hyaluronidase (type-I from bovine testes, Sigma, St Louis, MO) in PBS at 37˚C for 15 minutes. After washing, the samples were digested with 0.25% trypsin (type-I from bovine pancreas, Sigma) in PBS at 37˚C for 30 minutes, followed by digestion in DMEM containing 0.25% collagenase (type II, Sigma) on a gyrating shaker, until the tissue fragments were dissolved. Isolated cells were then washed with DMEM and cultured in DMEM containing 10% FCS and 50 µg/ml of L-ascorbate, 100 U/ml of penicillin and 100 µg/ml of streptomycin.

**Corticosteroid-induced apoptosis in cultured chondrocytes**

Corticosteroid-induced chondrocyte apoptosis was examined using flow cytometric analysis and TUNEL staining. For flow cytometric analysis, the cells were cultured with corticosteroid (hydrocortisone acetate, triamcinolone acetonide, dexamethasone: 10^{-5}M) for 12 hours, the cells in the control wells received PBS only. The concentration of corticosteroid (10^{-4}M) was chosen following the prior article (8). To analysis membrane changes associated with apoptosis, FITC-Annexin V binding to the cellular membrane, and PI staining of cellular DNA were performed as follows (18). After washing twice with PBS, 1 x 10^5 cells were re-suspended in binding buffer (10 mM Hepes/NaOH, pH 7.4, 140 mM NaCl, 2.5 mM CaCl_{2}). FITC–Annexin V was added at a final concentration of 1 µg/ml, and 0.1 volume of PI (10 µg/ml in binding buffer) was added to the cell suspension. The mixture was incubated for 10 minutes in the dark at room temperature, and the fluorescence was measured using a FACSscan.

To analysis the nuclear fragmentation with apoptosis, the cells were cultured with corticosteroid (hydrocortisone acetate, triamcinolone acetonide, dexamethasone acetate: 10^{-4}M) for 72 hours and fixed with 70% ethanol. After washing twice with PBS, 1 x 10^5 cells were stained with propidium iodide (PI) (1 µg/ml) and the ratio of fragmentation was measured using a FACSscan (Becton Dickinson Co., Mountain View, CA).

For TUNEL staining, chondrocytes were cultured with different doses of the corticosteroid (TA: 10^{-7} to 10^{-3} M) for 72 hours. We used TA to investigate the optimal concentration of induction chondrocyte apoptosis because TA has been widely used to intra-articular injection. The cells in the control wells received PBS only, and stained in the same manner as for the articular cartilage.

**Evaluation of the viability of cultured chondrocytes after corticosteroid administration (XTT assay)**

Chondrocyte viability was measured using the XTT (2,3-bis-[2-Methoxy-4-nitro-5-sulphophenyl]-2H-tetrazolium-5-carboxanilide) assay (19), as follows. Chondrocytes (1 x 10^4 cells/well) were seeded into 96-well flat-bottomed plates, and were incubated with various concentrations of corticosteroid (TA: 10^{-3} to 10^{-1} M) for 72 hours at 37˚C in a 5% CO_{2} atmosphere. The cells in the
control wells received PBS only. Next, the serum-containing medium was removed completely, and 200 µl/well of PBS was added. XTT (final concentration 200 µg/ml) and PMS (phenazine methosulfate, final concentration 5 µM) were added to each well. The chondrocytes were incubated for a further 4 hours, and the absorbance at 450 nm was measured by plate reader (BIO-RAD laboratories, Hercules, CA). XTT, in combination with PMS (electron-coupling agent), was metabolized by mitochondrial dehydrogenase enzymes of metabolically active cells. The cell viability was calculated as follows: Cell viability (%) = (OD450 of test sample – OD450 of background) / (OD450 of control sample – OD450 of background) x 100.

Statistical analysis
All data are expressed as means ± standard error of the mean (SEM). Welch’s correction test was used for statistical comparisons between groups. A p-value of less than 0.05 was considered to be statistically significant.

Results
Histological examination of the rabbit knee articular cartilage after different corticosteroids treatment
Corticosteroid-induced arthropathy was not observed in rabbit knee during this experiment. No remarkable change was observed in these cartilage by SO staining. TUNEL positive apoptotic cells were not increased in corticosteroid treated rabbit knee cartilage (Fig. 1).

Histological characteristics of the SCID mouse-implanted articular cartilage
Successful implantation of human articular cartilage was observed at 4 weeks following implantation. As we have reported previously (14-16), the implanted tissue was integrated into the back of the SCID mice, and the histological characteristics of the implanted tissue were similar to those of normal cartilage (Figure 2). The articular matrix was intensely stained by SO, and chondrocytes were observed in the lacunae. Apoptotic chondrocytes were not observed before corticosteroid treatment in TUNEL staining (data was not shown).

Histological examination of the articular cartilage and occurrence of chondrocyte apoptosis after corticosteroid treatment
SO staining could not reveal proteoglycan depletion at articular cartilage in the corticosteroid-treated animals (Figures 3A-3D). As shown in Figures 3E-3L, TUNEL staining of the implanted articular cartilage revealed that apoptotic chondrocytes were increased in the corticosteroid treated group compared with control group. (control: 0.5 ± 0.1/mm², hydrocortisone acetate: 12.1 ± 1.4/mm², triamcinolone acetonide: 9.4 ± 1.2/mm², dexamethasone acetate: 14.9 ± 1.7/mm² respectively: p < 0.05) (Table I). The appearance of apoptotic chondrocytes was further confirmed by electron microscopy (Fig. 4). Changes that are characteristic of apoptotic cells, including nuclear pigmentation and fragmentation and tightly packed cytoplasmic organelles, were observed after corticosteroid administration.

Corticosteroid induced apoptosis in cultured chondrocytes
Chondrocyte apoptosis was demonstrated by FITC-Annexin V / PI double staining. Phosphatidyl serine, which binds to Annexin V, translocates from the inner to the outer leaflet of the plasma membrane during an early event of apoptosis. Both FITC-Annexin V and PI negative viable cells were observed in the control groups (lower left quadrangle of Figure 5A). FITC-Annexin V positive and PI negative apoptotic cells, demonstrating Annexin V binding and cytoplasmic membrane integrity, were observed 12 hours after corticosteroid administration (lower right quadrangle of Fig. 5B-5D). These findings were observed all of three corticosteroids (B: hydrocortisone acetate, ...)
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Fig. 2. Articular cartilage grafted subcutaneously into SCID mice. At gross appearance (A: 4 weeks after implantation), neo-vascularization was observed at the grafted site and grafted cartilage was placed in the subcutaneous cavity (B). Histological characteristics of the implanted tissue remained similar to those of natural cartilage (C: HE staining, 11 weeks after implantation, original magnification x100. D: SO staining, 11 weeks after implantation, original magnification x100).

Fig. 3. Histological examination of implanted cartilage after corticosteroid treatment. Proteoglycan depletion was not remarkable in the corticosteroid-treated groups by SO staining (A: control; B: hydrocortisone acetate-treated group; C: triamcinolone acetonide-treated group; D: dexamethasone acetate-treated group. Original magnification x40). An increase of TUNEL-positive apoptotic cells can be clearly discerned after corticosteroid treatment (E, I: control; F, J: hydrocortisone acetate-treated group; G, K: triamcinolone acetonide-treated group; H, L: dexamethasone acetate-treated group. E-H: original magnification x40; I-J: original magnification x200).

C: triamcinolone acetonide, D: dexamethasone acetate: 10^{-4}M).

The induction of chondrocyte apoptosis was further confirmed by nuclear fragmentation. PI staining, with a shift to the left due to corticosteroid (hydrocortisone acetate, triamcinolone acetonide, dexamethasone acetate: 10^{-4}M) administration, suggests the appearance of DNA fragmentation in the cultured chondrocytes (Figs. 5E-5H).

In cultured chondrocytes, the number of TUNEL positive apoptotic cells was markedly increased by corticosteroid (TA: 10^{-4}M) administration compared with the control group (8.9 ± 1.2% versus 0.3 ± 0.05%, respectively; p< 0.05) (Fig. 6, Table II).

Decreased chondrocyte viability after corticosteroid administration

From the results of the XTT assay, it was shown that chondrocyte viability was decreased by corticosteroid administration (89.6 ± 3.1% at 10^{-4}M
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Table I. Number of TUNEL positive chondrocytes in the grafted human articular cartilage on the back of SCID mouse after different corticosteroids treatment.

<table>
<thead>
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<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
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<tr>
<td>TUNEL positive chondrocytes (/mm²)</td>
<td>0.5±0.1</td>
<td>12.1±1.4*</td>
<td>9.4±1.2*</td>
<td>14.9±1.7*</td>
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A: control (PBS: 0.2ml)
B: hydrocortisone acetate: 1mg/0.2ml
C: triamcinolone acetonide: 0.2mg/0.2ml
D: dexamethasone acetate: 0.1mg/0.2ml
Values are mean ± SEM. *: p<0.05 compared to control (PBS) group.

Discussion

In this study, we observed chondrocyte apoptosis after corticosteroid treatment in vivo and in vitro. Repeated intra-articular corticosteroid injections are known to result in a progressive degradation of articular cartilage and joint destruction (2). This steroid-induced arthropathy may result from the down regulation of matrix synthesis in cartilage after corticosteroid treatment (20). But steroid-induced arthropathy brings irreversible changes to the articular cartilage even though intra-articular steroid injection has been cancelled. So we hypothesized cartilage degradation was associated with chondrocyte apoptosis. And chondrocyte apoptosis may play an important role in steroid-induced arthropathy. In fact, chondrocyte apoptosis has been implicated previously in other diseases, including RA.

Fig. 4. Electron microscopic examination of the chondrocyte after corticosteroid treatment. Nuclear pigmentation, fragmentation, and tightly packed cytoplasmic organelles were observed by electron microscopic examination in the corticosteroid-treated group (A: control; B: triamcinolone acetonide-treated group, original magnification x10000).

Fig. 5. Flow cytometric analysis of the cultured chondrocytes. By double staining of FITC-Annexin V / PI, FITC-Annexin V-positive PI-negative apoptotic cells was observed in the lower right quadrant (B-D) after corticosteroid administration at 12 hours (A: control; B: hydrocortisone acetate 10⁻⁴M; C: triamcinolone acetonide 10⁻⁴M; D: dexamethasone 10⁻⁴M). After 72 hours of corticosteroid administration exhibit fragmented nuclei, as indicated by the presence of a left-shifted peak (A: control; B: hydrocortisone acetate 10⁻⁴M; C: triamcinolone acetonide 10⁻⁴M; D: dexamethasone 10⁻¹M).
Fig. 6. TUNEL staining of cultured chondrocytes. At low dose of corticosteroid, it was not observed the remarkable increasing of TUNEL positive apoptotic cells. At high dose (10^{-7}M, 10^{-6}M) statistically significant increasing was observed compared with control (A: control PBS; B: after 72 hours 10^{-7}M triamcinolone acetonide; C: 10^{-6}M; D: 10^{-5}M; E: 10^{-4}M; F: 10^{-3}M. Original magnification x100).

Table II. Percentage of TUNEL positive cells in the cultured chondrocyte with the indicated dose of Triamcinolone acetonide (TA) (0, 10^{-7}, 10^{-6}, 10^{-5}, 10^{-4}, 10^{-3}M).

<table>
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<tr>
<th>Concentration of TA (M)</th>
<th>0</th>
<th>10^{-7}</th>
<th>10^{-6}</th>
<th>10^{-5}</th>
<th>10^{-4}</th>
<th>10^{-3}</th>
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<tbody>
<tr>
<td>TUNEL positive cells (%)</td>
<td>0.3±0.05</td>
<td>0.5±0.1</td>
<td>2.2±0.5</td>
<td>4.0±0.7</td>
<td>8.9±1.2*</td>
<td>14.3±1.1*</td>
</tr>
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</table>

Values are mean ± SEM. *: p<0.05 compared to control (PBS) group.

Table III. Viability of the cultured chondrocytes with the indicated dose of Triamcinolone acetonide (TA) (0, 10^{-7}, 10^{-6}, 10^{-5}, 10^{-4}, 10^{-3}M).

<table>
<thead>
<tr>
<th>Concentration of TA (M)</th>
<th>0</th>
<th>10^{-7}</th>
<th>10^{-6}</th>
<th>10^{-5}</th>
<th>10^{-4}</th>
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<tbody>
<tr>
<td>Viability (%)</td>
<td>100</td>
<td>102.2±1.7</td>
<td>94.8±2.3</td>
<td>91.6±2.9</td>
<td>89.6±3.1</td>
<td>74.3±4.2*</td>
</tr>
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Values are mean ± SEM. *: p<0.05 compared to control (PBS) group.

and OA (10-13), and this process may be linked to arthropathy (13). Chondrocyte apoptosis is observed in the corticosteroid-induced arthropathy knee in human (Fig. 7). But because these cartilages were worn out, it was remained unclear whether chondrocyte apoptosis had been induced by corticosteroid injection or by mechanical stress. Recently it was reported that apoptotic cell death is not a widespread phenomenon in normal aging and osteoarthritic human articular knee cartilage (21). We also observed that chondrocyte apoptosis is not seen in the comparatively normal cartilage after intra-articular corticosteroid injection in human knee. So that we used animal model to examine the mechanism of steroid-induced arthropathy. Several animal experiments were undertaken to study the effects of cartilage damages caused by repeated intra-articular injection of corticosteroids (22, 23). These reports demonstrated proteoglycan loss and fissures and cysts in articular cartilage. But they did not mention empty lacunae in the articular cartilage in those animal models. It might be important to invest the chondrocyte viability before the breakdown of articular matrix. Because we could not make corticosteroid-induced arthropathy in healthy rabbit knee by corticosteroid injection, in this experiment we used SCID/hu model. It was obscure why the corticosteroid-induced arthropathy was not observed in the rabbit knee in our experiment. It might cause of the difference of experimental condition and period. If we had used much volume of corticosteroid and injected more often times and more long term, it might have been observed corticosteroid-induced arthropathy. But if so, it would include mechanical injury among the result of experiment. We believe that our experimental condition was appropriate to evaluate the articular chondrocyte apoptosis induced by corticosteroid. In SCID/hu model human articular cartilage was maintained the characteristics of in vivo human cartilage and injected corticosteroid remained prolonged period in
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the subcutaneous cavity. And more in this model, without any confounding mechanical influences, destructed grafted cartilage was not observed and proteoglycan loss was not remarkable. These findings also indicate that chondrocyte apoptosis was not induced by wound or mechanical stress but by corticosteroid treatment.

In the cultured chondrocytes, few apoptotic cells were observed at low doses of corticosteroid. However chondrocytes apoptosis was observed at the high dose of corticosteroid (1 x 10^4 M) which can be achieved clinically by intra-articular injection. For the above reasons, we conclude that weekly high dose corticosteroid injection may induce chondrocyte apoptosis. In this article three different corticosteroids (hydrocortisone acetate, triamcinolone acetonide, dexamethasone acetate) were used. Though statistical significance change was not observed among these corticosteroids, dexamethasone acetate was most effective to induce the chondrocyte apoptosis. The difference of effect of apoptosis induction might be caused by binding affinity to glucocorticoid receptor. It was reported that cartilage in the growth plate is induced apoptosis by glucocorticoid via glucocorticoid receptor (8). And chondrocyte apoptosis might be regulated by corticosteroid by decreasing bcl-2 and increasing Bax (24). Articular chondrocyte apoptosis might be induced by same mechanism that induced via glucocorticoid receptor and regulated by decreasing bcl-2 and increasing Bax.

In conclusion, we have examined a possible mechanism of steroid-induced arthropathy using SCID/hu model that was engrafted with human articular cartilage, and using an in vitro human chondrocyte culture. Our results indicate that corticosteroid administration induces the apoptosis of chondrocytes. These findings are important for our understanding of the articular cartilage degradation process following corticosteroid administration.

References


