WONDER WHY?

A SCIENTIFIC EDITORIAL

The Deterioration of Articular Cartilage in Osteoarthritis by Corticosteroid Injections

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ABSTRACT

The hallmark feature of osteoarthritis is the breakdown in the articular cartilage of joints such as the knee and hip. Both animal and human research has consistently shown that corticosteroid injections into normal and degenerated knees accelerate the arthritic process. A summary of the effects of the intraarticular cortico-steroids on articular cartilage includes: a decrease of protein and matrix synthesis, matrix hyaline appearance becomes fibrotic, clumping of collagen, alteration in chondrocyte cell shape, chondrocyte cell proliferation inhibited, chondrocyte cytoxicity enhanced, loss of chondrocytes, surface deterioration including edema, pitting, shredding, ulceration and erosions, inhibition of articular cartilage metabolism, articular cartilage necrosis, thinning of articular cartilage, decrease in cartilage growth and repair, formation of articular cartilage cysts, and ultimately articular cartilage destruction.

When researchers microscopically and radiologically examine human joints after corticosteroid injections, the same results are found in humans as in animals. Intraarticular corticosteroid injections accelerate the osteoarthritic degenerative process. Because of this possibility, organizations such as the American College of Rheumatology acknowledge, "It is generally recommended, although not well supported by published data, that injection of corticosteroids in a given joint not be performed more than three to four times in a given year because of concern about the possible development of progressive cartilage damage through repeated injection in the weight-bearing joints." It is this author's opinion that there is no doubt that the rise of osteoarthritis, as well as the number of hip and knee replacements, is a direct result of the injection of corticosteroids into these joints.

Osteoarthritis (OA) is a major cause of pain and disability, as well as cost, to both the individual and society. The average direct out-of-pocket expenditure of OA is approximately $2600 per person per year, but the total annual cost per person (including lost productivity) is between $5700 and $9600.[1,2] OA and related conditions cost the U.S. economy nearly $128 billion per year in medical care and indirect expenses, including lost wages and productivity.[3] A major component of the economic burden associated with the treatment of arthritis relates to surgical joint replacements of the hips and knees. In 2004, the national bill of hospital charges for hip/knee replacements was $26 billion, and the hospital cost was $9.1 billion.[4] Musculoskeletal procedures, including hip and knee replacements, account for ten percent of all hospital care in the United States. From 1997 to 2005, the number of knee replacements climbed by 69 percent, from 328,000 to 555,800. The number of hip replacements rose from 290,700 to 383,500 procedures.[5] The number of these procedures is increasing at an alarming rate. Nearly 600,000 hip replacements and 1.4 million knee replacements will be performed in the year 2015.[6] By 2030, it is estimated that the number of hip and knee replacements annually will increase to 1.85 and 3.48 million, respectively.[7] (*See Figure 1.*) The question to ask is why has there been such an alarming rate of articular cartilage deterioration necessitating all of these joint replacements? What is causing it?

OA currently affects more than 27 million Americans, up from 21 million in 1990. By the year 2030, it is expected that more than 67 million Americans will have arthritis.[8] (*See Figure 2.*) While much is known about what happens at the level of the joint after the start of OA, there is no consensus as to why the condition starts in the first place. Factors influencing the incidence of OA have been identified through epidemiological and small group studies. These factors include sex (women, especially after entering menopause), low hormone levels,

Figure 1. Escalation in incidence of knee and hip replacements in the US. By 2030, hip replacement numbers could reach 1.85 million and knee replacements reach 3.48 million.
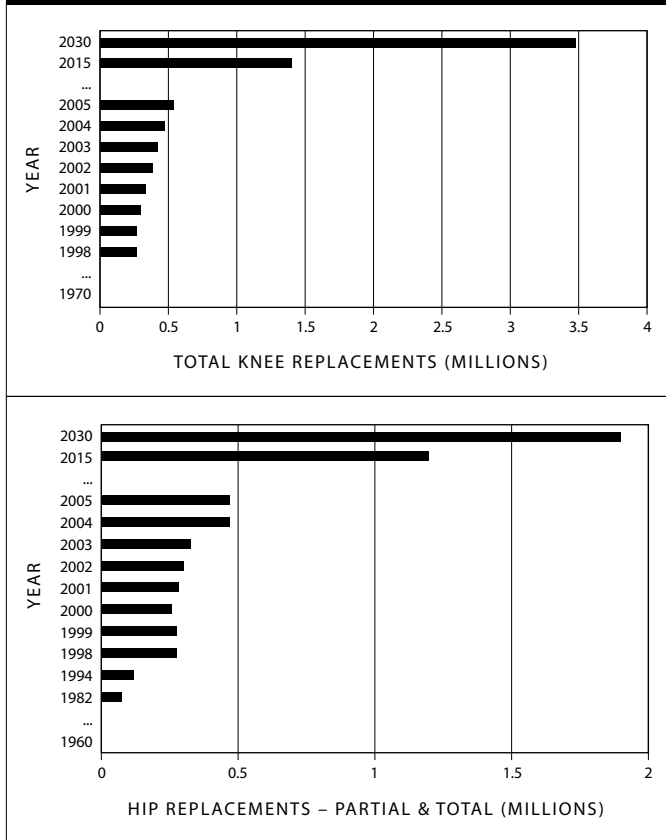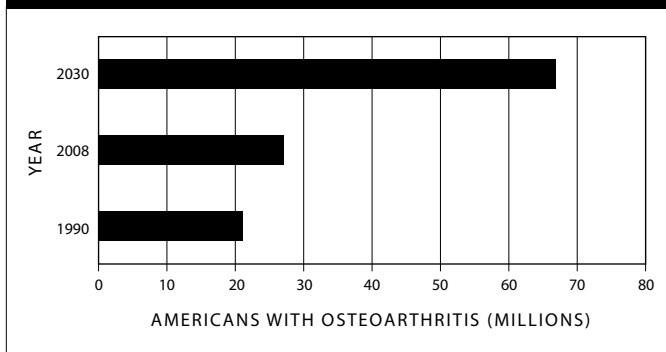

Figure 2. Osteoarthritis incidence in the United States. By the year 2030 it is estimated that the number of Americans suffering from osteoarthritis could reach as high as 67 million.

nutritional factors, obesity, inheritance, knee injury, quadriceps strength, ligament laxity, and joint injury due to misalignment, overload or trauma.[9-11] While many of these have been well studied, it is doubtful that they alone could account for the dramatic rise in OA over the last forty years, and the predictions of OA in epidemic proportions for the near future.

The hallmark feature of OA is a breakdown in the articular cartilage of joints such as the knee and hip. The articular cartilage covers the connecting surfaces of two bones where they join, allowing them to glide effortlessly, one bone over the other. The first feature of OA is a fraying and fibrillation of the articular cartilage surface. (*See Figure 3*.) This coincides with a loss of proteoglycans from the matrix of articular cartilage.[12] Articular cartilage contains chondrocytes embedded in an extracellular matrix composed primarily of type II collagen and proteoglycans. Articular cartilage bulk chemical analysis reveals that it is composed of 10 to 15 percent collagen, 10 to 15 percent protein polysaccharide (proteoglycan), and 70 to 80 percent water.[13] Chondrocytes make up one to five percent of the volume in adult cartilage tissue. Chondrocytes are the cells responsible for the formation, maintenance, and repair, of articular cartilage.[14] Despite a poor oxygen tension, limited nutrient supply, and anaerobic metabolism, chondrocytes can still produce large amounts of collagen and proteoglycans.[15] The collagen provides strength to the cartilage, the proteoglycans provide elasticity and stiffness on compression. The proteoglycans are very hydrophilic, meaning they are attracted to water. The proteoglycans form aggregates, which give articular cartilage its unique abilities to act as a shock absorber for joints such as the knee and hip.[16] (*See Figure 4.*)

OA begins immediately once chondrocyte function is altered. This leads to a decrease in the ground substance, or proteoglycans. This weakens the cartilage structure. The cartilage breaks down further causing fissures in it. Eventually there is enough breakdown of the cartilage that it can be seen on X-ray as joint space narrowing. This causes a transmission of pressures that are too high for the bones to handle. Eventually the space between the bones becomes completely obliterated. This is when the orthopedic surgeon tells the patient he/she has bone on bone and needs a joint replacement. (*See Figure 5.*)

Early in the course of OA, the tissue mounts an attempt at repair. Chondrocytes proliferate with a resulting increase in matrix synthesis. However, in the face of chronic mechanical degenerative forces, degradative enzymes overwhelm the synthetic capability. The net result is too much degradation of cartilage and not enough repair. Traditional pharmacological treatments, including non-steroidal anti-inflammatory drugs and corticosteroids shots, are typically used to not only decrease symptoms, but also to hopefully improve the physiology of the
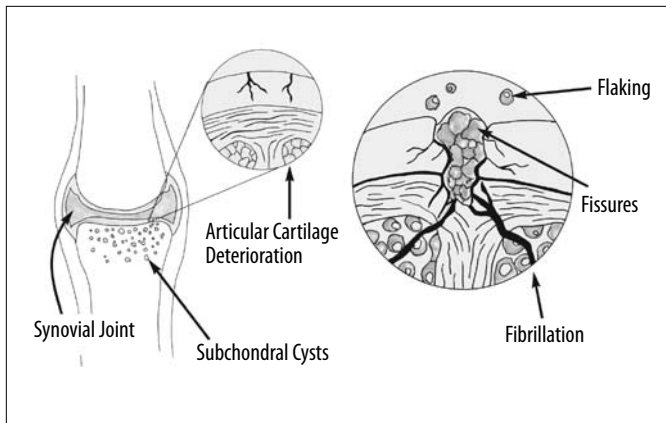
Figure 3. Pathogenesis of arthritis. Articular cartilage deterioration as evidenced by fibrillation, fissures, and flaking.

Used with permission from *Prolo Your Pain Away! Curing Chronic Pain with Prolotherapy*, Third Edition; Ross A. Hauser, et al. Beulah Land Press, 2007, Oak Park, IL.

Figure 4. Proteoglycan aggregate. The proteoglycans attract water and give articular cartilage its "shock absorbing" properties.

Used with permission from *Prolo Your Sports Injuries Away! Curing Sports Injuries and Enhancing Athletic Performance with Prolotherapy*, Ross A. Hauser, et al. Beulah Land Press, 2001, Oak Park, IL.

disease process. Unfortunately the preponderance of evidence shows that these treatments actually *accelerate the osteoarthritic process*.[17,18] The rest of this paper will focus on the evidence that corticosteroids deteriorate normal and degenerated articular cartilage.

Intraarticular injections of corticosteroids have been used for the treatment of OA of the knee and other joints for more than 50 years, but there is little controlled evidence to support their use.[19-22] Since 1951, when Thorn first injected hydrocortisone into the knee joint of a patient with rheumatoid arthritis, the anti-inflammatory effects of intraarticular corticosteroid compounds have been established.[23] Cortisol, and the synthetic analogs of cortisol, have the capacity to prevent or suppress the development of the local heat, redness, swelling, and tenderness, by which inflammation is recognized. At the microscopic level, they inhibit not only the early phenomena of the inflammatory process, edema, fibrin deposition, capillary dilatation, migration of leukocytes into the inflamed area, and phagocytic activity, but also the later manifestations of capillary proliferation, fibroblastic proliferation, deposition of collagen, and still later, cicatrization.[24]

The first evidences that steroids injected locally produced adverse effects came a few years after doctors started using

> **cicatrization** – the process whereby wound healing forms scar tissue.
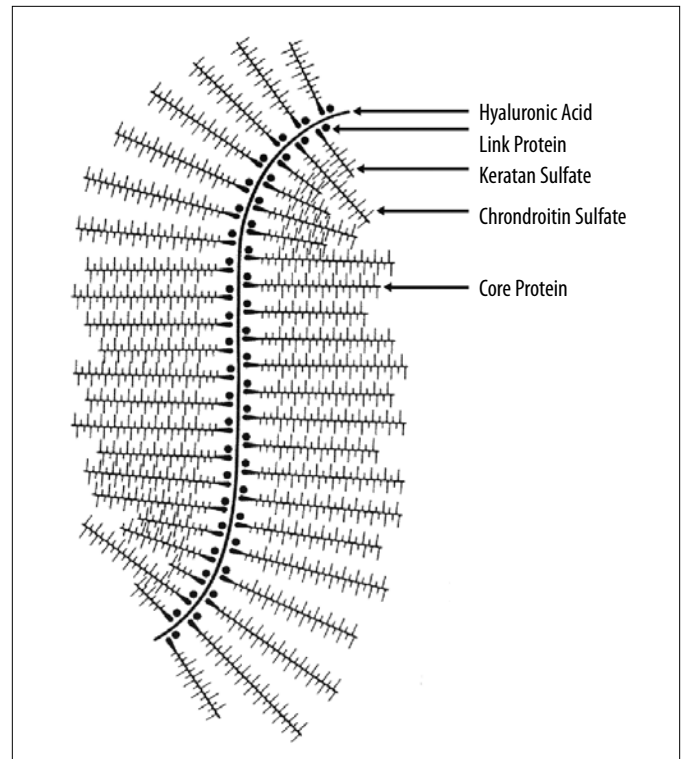
corticosteroids. Several case studies reported rapidly progressive degenerative arthritis following intraarticular hydrocortisone injections.[25-27] Researchers then started looking at intraarticular corticosteroid injected joints in

Figure 5. X-ray of a severely degenerated hip. No cartilage remains in this left hip joint, thus this patient would be a candidate for a hip replacement.

animals, comparing them to similar joints injected with saline (control). The feeling was that these studies should provide a useful indication of the clinical effects of these drugs on normal or diseased joints in man.

ANIMAL STUDIES

It is well known and accepted that medications must first be shown to be safe in animals before they are given or injected into human beings. It is also much easier to study the effects of the drugs, or injection of the drugs, in animals because the animals can be sacrificed, and the tissues examined under a microscope. This allows the researcher to evaluate not only the potential beneficial effect of the medication, but also detrimental effects.

Using tritiated glycine (glycine ^{3}H) as an indicator of amino acid incorporation in protein synthesis in cartilage matrices, Mankin and Conger injected hydrocortisone acetate into rabbit knees. Their data showed a rapid and profound decrease in glycine incorporation that appeared to depend on dosages. Maximum decline was seen six hours after the injection.[28] They did a similar experiment using glycine ^{14}C as the radiotracer, which showed a definite decrease in the rate of protein synthesis within two hours of the injection. They noted that the rate of the inhibitory effect of intraarticular hydrocortisone on cartilage protein synthesis was about twice that of the observed rate for corticosteroids given by intramuscular route.[29] One year later, researchers injected hydrocortisone into normal rabbit knees and produced thinning of the cartilage, and the development of fissures and fibrillations in the articular cartilage. They also found multiple small white deposits within the substance of the articular cartilage, which were found to represent cystic areas of degeneration within the middle zone of the cartilage matrix. These effects were most marked in the animals which had the greatest number of injections.[30] Deleterious effects of cortisone were reported by some

> **They noted that the rate of the inhibitory effect of intraarticular hydrocortisone on cartilage protein synthesis was about twice that of the observed rate for corticosteroids given by intramuscular route.**

> **"It must be expected that corticosteroids can retard or prevent recovery in naturally occurring joint diseases. Administration of these drugs must therefore be considered with caution."**

researchers who noted that the drug inhibited the synthesis and deposition of chondroitin sulfate in cartilage.[31-33] Many research papers have documented that corticosteroids reduced radiosulfate uptake into chondroitin sulfate, thereby decreasing cartilage growth and repair.[34-37] Other research on the articular cartilage of rabbits showed that the destruction of articular cartilage by corticosteroids worsened with time. Microscopic degenerative changes were progressively more evident, including loss of protein polysaccharide in the matrix, decreased number of chondrocytes, loss of cell shape, distortion of the cell membrane and nucleus leading to chondrocyte degeneration, multiple fissuring of the matrix, clumping of collagen, and finally by the sixth month, appearance of large cysts containing debris and degenerated chondrocytes.[38-41] (*See Figure 6.*)

In regard to the progression of OA, is the articular cartilage damage seen from the disease or from the steroid injection treatments? One research paper put it this way: "After administration of corticosteroids to patients suffering from arthritis, it is impossible to decide how much damage is due to the steroids and how much is due to the natural progress of the disease. To answer this question, these researchers devised a study to look at what happens to rabbit articular cartilage subjected to corticosteroid concentrations compatible with what we observed in human patients. They compared this group to normal control animals who received no injections. They also induced an artificial arthritis in one group of animals, used them as another control, and saw what happened to some of these animals if they also were subjected to low dose corticosteroids. Compared to the control groups, the corticosteroids caused severe deleterious effects on the articular cartilage. The articular cartilage became thin, the matrix near the surface lost its hyaline appearance and became fibrous, the surface fibrillated, and the arthritic cartilage lost its ability to repair itself. This last effect caused the researchers to state "It must be expected that
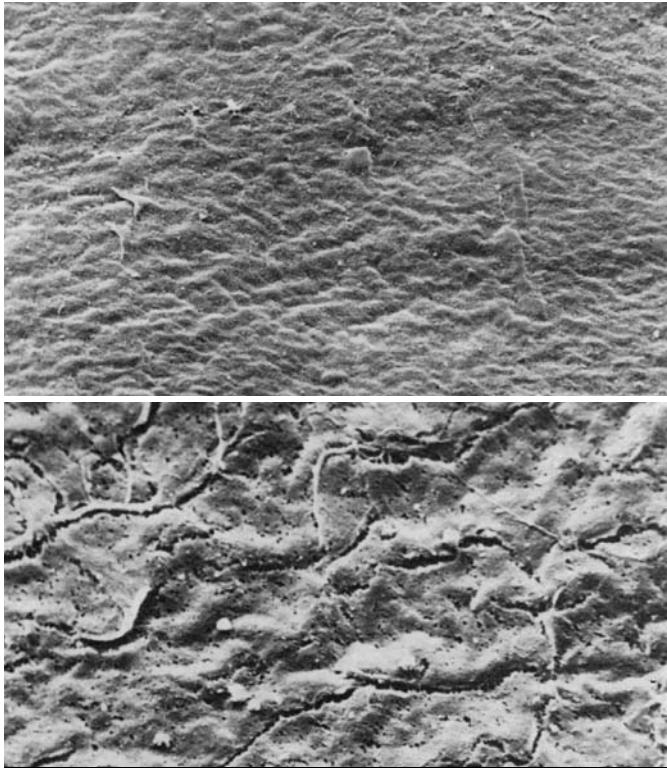
Figure 6. Electronmicroscopy of articular cartilage after saline injections versus corticosteriod injections. Articular cartilage injected with saline has a normal, smooth appearance (top), whereas corticosteroid injected cartilage has obvious fissuring and is in the process of deteriorating (bottom).

Pictures originally from the *Journal of Anatomy*, volume 127, Oct. 1978, pages 393-402. Article title: Effects of intraarticularly administered corticosteriods and salicylates on the surface structure of articular cartilage.

corticosteroids can retard or prevent recovery in naturally occurring joint diseases. Administration of these drugs must therefore be considered with caution."[42] This last quote was written in 1973. For this review I purposely used "old" research to emphasize the point that the effects of corticosteroids have been known for years. Current research done in 2007 on rabbit cartilage continues to confirm that corticosteroid injections into the knee joints of rabbits causes cartilage necrosis.[43]

CORTICOSTEROIDS INDUCE PREMATURE CELL DEATH OF CHONDROCYTES IN ARTICULAR CARTILAGE

Dexamethasone is a corticosteroid commonly used in humans and domestic animals, particularly in the treatment of painful conditions. When articular cartilage cells were subjected to dexamethasone, cell proliferation was inhibited. Even more significant than that was the fact that dexamethasone induced cell apoptosis.[44] Apoptosis is a form of programmed cell death. In simple terms,

dexamethasone caused chondrocytes to die a premature death. The mechanism by which corticosteroids does this is most likely through blocking the anti-apoptotic effects of Insulin-like growth factor (IGF-1).[45,46]

DETERIORATION OF ARTICULAR CARTILAGE WITH JUST ONE STEROID INJECTION

Regarding the effect of corticosteroid injections, some researchers started looking at the effects of *just one* corticosteroid injection into a joint of an animal. One study, done at University Central Hospital in Helsinki, Finland, showed significant deleterious effects on cartilage via electron microscopy after only one steroid injection into the knee. The authors also found that the higher the dose of steroids injected into the knee, the worse the deterioration.[47] Even one injection into the temporomandibular joint (TMJ) showed tremendous destruction of the articular cartilage and underlying bone.[48] Another study showed that even 16 weeks after a single steroid joint injection, the cartilage remained biochemically and metabolically impaired.[49]

CORTICOSTEROIDS CAUSE CARTILAGE DETERIORATION IN EXERCISED HORSES

Corticosteroid injections into equine (horse) joints cause similar effects as those in the rabbit. Equine research has been consistent in that corticosteroids cause a breakdown of the cartilage matrix and protein synthesis.[50-52] It is especially damaging to pony foals where corticosteroids caused joint damage either at the joint surface or deep within the cartilage. Signs of surface deterioration included edema, fibrillation, enlargement of lacunae, pitting, and shredding and erosions of the cartilage. Cartilage ulceration and fracture was common. Glycosaminoglycan content of articular cartilage decreased by 55% in three months. Corticosteroids inhibited articular chondrocyte metabolism which initiated cartilage degeneration. Surface destruction and osteochondrosis dissecans followed continued mechanical stress of compromised cartilage.[53] (*See Figure 7.*) In another study, articular cartilage and chondrocytes obtained from young adult

> **Osteochondrosis dissecans** – *a disorder in which a fragment of cartilage and subchondral bone separates from an articular surface.*

horses ages 1.5–3.5 years of age were subjected to the corticosteroid methylprednisolone. Chondrocyte cytotoxicity was found as the steroid concentration was

Figure 7. Knee joint with articular cartilage fragment missing. Severe damage to articular cartilage surfaces can occur with corticosteroid injections which can be localized as the above picture captures.

increased. This coincided with a decreased and altered chondrocyte expression of matrix proteins, which the authors felt likely contributed to the pathogenesis of corticosteroid-induced cartilage degeneration.[54] Researchers at the University of Montreal showed that repeated intraarticular injections into the radiocarpal joint of horses free of OA, compared to controls, induced the breakdown of articular cartilage. Specifically, the biomarkers for proteoglycan and collagen breakdown were significantly elevated in the corticosteroid injected joint fluid.[55] In a similar experiment, chromatographic analysis of joint fluid in corticosteroid injected joints showed fragments of the articular cartilage aggrecan. They were significantly elevated in the steroid injected joints, compared to control joints. The authors summarized their findings by saying, "these results indicate that the repeated use of intraarticular methylprednisolone acetate leads to potentially harmful inhibition of procollagen II synthesis and an increased release of degradation products of the proteoglycan aggrecan from articular cartilage."[56] To see what happens when you inject steroids into a joint and then exercise the joint, researchers at Kansas State University injected the contralateral middle carpal joints of healthy horses with either corticosteroid or diluents (control). The results showed that steroid injected cartilage was 24% thinner and had a 97% decrease in compressive stiffness. The authors concluded that repetitive intraarticular administration of corticosteroid in exercising horses alters the mechanical integrity of articular cartilage.[57] A summary of the effects of the intraarticular corticosteroids as denoted by the above research can be seen in Table 1. (*See Table 1.*)

HUMAN DATA

Temporary and permanent damaging changes in soft tissue, bone, and cartilaginous structures, have long been reported to occur when corticosteroids are administered for human disease.[58-62] In my pain practice, it is relatively common for a person to come in with X-rays or MRIs which demonstrate a rapid deterioration of the articular cartilage after being on a strong anti-inflammatory medication or receiving a corticosteroid shot. (*See Figure 8.*) One of the first reports of corticosteroid-induced cartilage damage was in 1960, where the authors reported on four cases of steroid arthropathy after patients were given corticosteroids.[63] The authors noted, "Rapid destruction of the femoral head with subsequent disorganization of the hip joint rarely, if ever, occurs in uncomplicated rheumatoid arthritis or osteoarthritis. Recently we have seen four patients, all treated with corticosteroids, in which such destruction developed. The striking feature in each case was the relative freedom from pain in the presence of severe joint disorganization. Before advising treatment with either oral or intraarticular administration of corticosteroid, this possible complication should be borne in mind, and the likelihood of accelerated joint destruction weighed against the benefit which the patient is likely to derive." There are many other reports of corticosteroids dramatically accelerating the arthritic

Table 1. Known effects of intraarticular corticosteroids on articular cartilage.

- Deleterious effects more serious in animals with the greatest number of injections
- Higher dose leads to worse deterioration
- Destruction worsened with time and exercise
- Inhibition of synthesis and deposition of chondroitin sulfate and glycosaminoglycan
- Breakdown of proteoglycans and collagen
- Decrease of protein and matrix synthesis
- Matrix hyaline appearance becomes fibrous
- Clumping of collagen
- Alteration in chondrocyte cell shape
- Chondrocyte cell proliferation inhibited
- Chondrocyte cytotoxicity enhanced
- Loss of chondrocytes
- Surface deterioration including edema, pitting, shredding, ulceration and erosions
- Inhibition of articular cartilage metabolism
- Articular cartilage necrosis
- Thinning of articular cartilage
- Decrease of cartilage growth and repair
- Formation of articular cartilage cysts
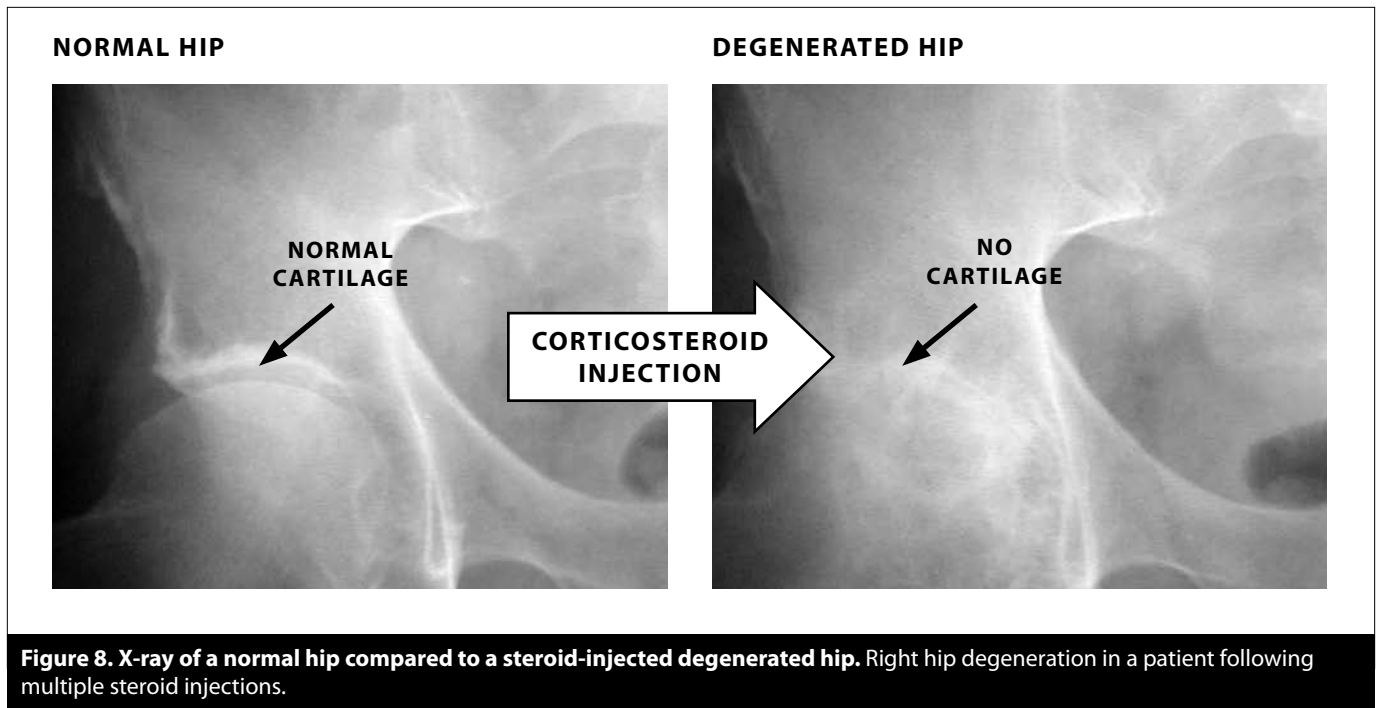- Articular cartilage destruction

NORMAL HIP

DEGENERATED HIP

NORMAL CARTILAGE

CORTICOSTEROID INJECTION

NO CARTILAGE

Figure 8. X-ray of a normal hip compared to a steroid-injected degenerated hip. Right hip degeneration in a patient following multiple steroid injections.

process.[63-67] The current literature continues to report on papers whereby intraarticular corticosteroid injections cause this rapid destruction of articular cartilage in various joints including the hips and shoulders.[68-71]

Corticosteroids are injected into joints because they often provide some pain relief. Perhaps it is just this effect, however, that is one of the main reasons corticosteroids deteriorate cartilage. The thought process is simple. A person receives an intraarticular corticosteroid injection because of an injury within and/or around, the involved joint. The corticosteroid provides pain relief, generally lasting for a few weeks. So, some of the articular cartilage damage from steroids can be attributed to analgesia, resulting in microtrauma due to painless overuse. During the period of pain relief offered by the steroid shot, the person resumes normal activities, including athletics. Without the steroid, the person is unable to perform these activities or they are modified because of pain. Now, because the patient does not sense the pain, activities are resumed. This situation is much like the professional football players who receive steroid injections before or during an NFL game. A recent Caring Medical patient told me that during a typical NFL game, five players are receiving injections before or during a game. He said that he has even received two shots in one game. (*See Figure 9.*) Without a pain signal, the patient has no idea if the activities he is doing, such as running and jumping, are contributing to the deterioration of his cartilage.

Another good example of painless cartilage deterioration is rheumatoid arthritis. Three papers clearly demonstrate the principle that cartilage could be deteriorating even though, clinically, a patient feels better. In the first study involving forty rheumatoid arthritis patients, patients reported feeling better due to medications including steroids, with resultant improvement in their blood tests as well. However, X-rays of their hands and feet over the years revealed worsening of the cartilage.[72] In cases where the patients' rheumatoid arthritis was in complete remission, researchers found that even though the rheumatoid

Figure 9. Steroid injections temporarily block the pain signal. Without a pain signal, the patient (athlete) cannot determine whether their activities, such as running or jumping, are contributing to cartilage deterioration because the steroid has masked the pain.

arthritis was in clinical remission, articular cartilage deterioration was still reported.[73,74] Simply put, pain is our protective mechanism to know something is wrong. Blocking the pain response with anti-inflammatories or corticosteroids overrides this mechanism. Cortisone shots and exercise can be a deadly combination for articular cartilage cells. A good example of this was an animal study where the researchers looked at cartilage cell counts in hydrocortisone injected knees without exercise and those in hydrocortisone injected knees with exercise. This would be akin to patients receiving cortisone shots so they could resume their tennis playing. In this study, all knees injected with cortisone showed cartilage deterioration, but severe cartilage damage was seen in 67% of animals that exercised and also received cortisone. The cortisone and exercise group also showed a significant decline in glycosaminoglycan synthesis and cartilage cell counts compared to the other group. The animals that received a cortisone shot and then ran showed areas of cartilage cell death, which weren't seen in those animals that only exercised or only received a cortisone shot.[75] (*See Figure 10.*)

ARTICULAR CARTILAGE DETERIORATION NOT DUE TO AGING

By the time the first changes of radiological osteoarthritis are detected, 13% of knee cartilage has already been lost.[76] Articular cartilage volume normally decreases by two to three percent per year.[77] Researchers have already shown that lifelong moderate use of normal joints does not increase the risk of OA.[78-80] The degeneration of normal articular cartilage is not simply the result of aging and mechanical wear. Once OA forms, articular cartilage volume decreases at a rate of about four to five percent per year.[81-83] The rate of loss at two years predicts subsequent total knee arthroplasty. For every one percent increase in the rate of tibial cartilage loss there was a 20% increase risk for undergoing a knee replacement at four years.[84] Surely we all should be asking the question *what is causing this increase in tibial (joint) cartilage loss beyond that occurring with the normal aging process?* Could it be the actual anti-inflammatory medications used by doctors to treat osteoarthritis?

While it is easier to microscopically study the effects of intraarticular corticosteroids in animals and compare them to non-injected joints because animals can be sacrificed, the same is not so in humans. For this reason, less human data exists, but what is available is compelling. *Intrarticular corticosteroids accelerate human articular cartilage deterioration just like in animals.*
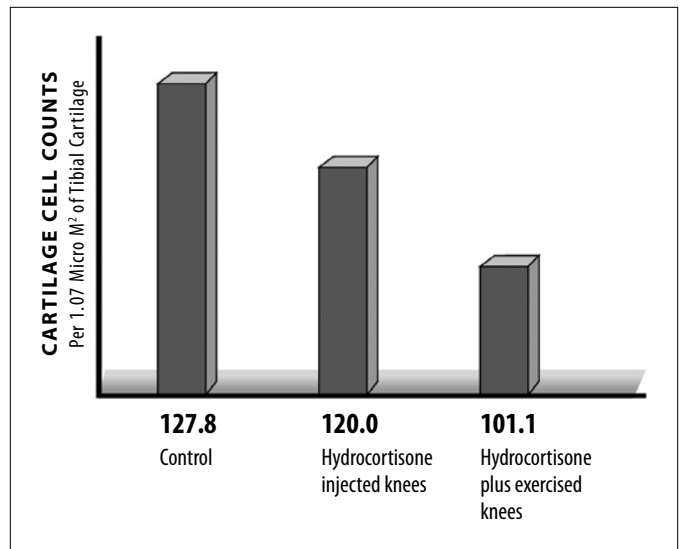

Figure 10. Cartilage cell counts decline with cortisone plus exercise. Hydrocortisone injections in the knee combined with exercise is a deadly combination for cartilage cells.

Used with permission from *Prolo Your Sports Injuries Away! Curing Sports Injuries and Enhancing Athletic Performance with Prolotherapy*, Ross A. Hauser, et al. Beulah Land Press, 2001, Oak Park, IL.

NATURAL COURSE OF OSTEOARTHRITIS OF THE KNEE TREATED WITH OR WITHOUT INTRAARTICULAR CORTICOSTEROID INJECTIONS

This heading was the title of an article published in 1993, that compared osteoarthritic knees treated with intraarticular corticosteroid injections to those treated without them.[85] The research was done by four doctors in the Department of Orthopaedic Surgery at Yokohama City University School of Medicine in Yokohama, Japan. They were able to analyze X-rays, pain levels, and functional status of the patients at the start of treatment and after a ten-year period.
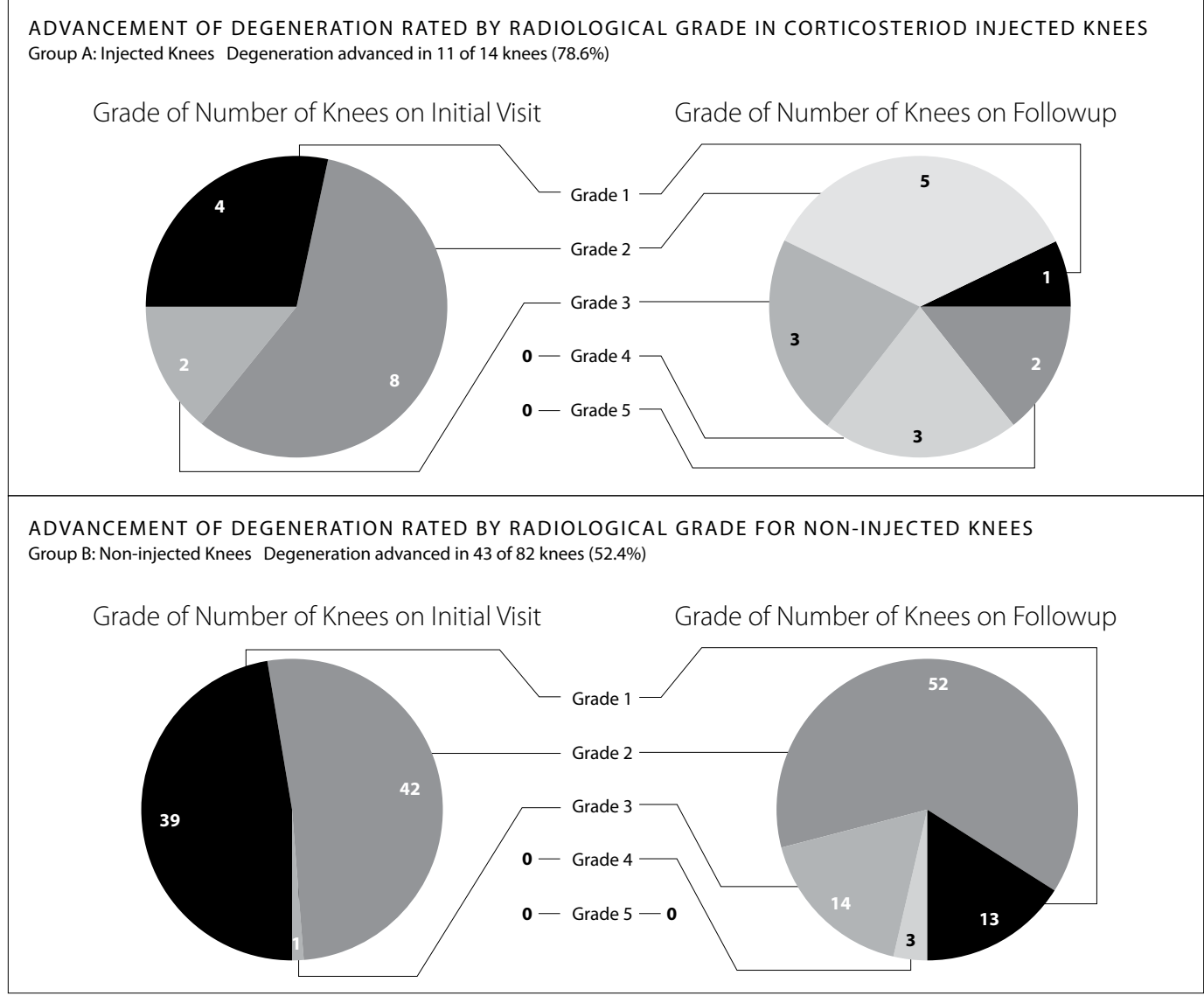
The 82 knees not receiving corticosteroid injections were compared to the 14 knees that did receive them. The average age of the patients at the beginning of the study was 60 years-old, and at the end, 70. The median number of corticosteroid injections per joint was 25. Limb alignment was evaluated at the femorotibial angle, measured via an anteroposterior radiograph taken with the patient standing on one leg. The angle is the lateral angle between the femoral axis and the tibial axis. The results of the study revealed a significant difference in the femorotibital angle before and after the corticosteroid injections in the knees of the male patients. Specifically these knees went from 0.6 degrees of valgus at the initial visit, to a varus-angulation of 3.4 degrees.

The osteoarthritis of each of the knees was classified into six grades, varying from Grade 0 (normal) to Grade 5 (severe bony defects) using the standing radiograph. (*See Table 2.*) In the corticosteroid-treated group, degeneration of the knee joint associated with bony defects equivalent to Grade 4 or 5 was found in five of fourteen knees, but this was only seen in three of 82 knees that received no injections. (*See Table 3.*) Radiographic degeneration was observed to be more advanced in the group that received corticosteroid injections than in the group that did not receive such injections. In the corticosteroid-injected knees, the radiographic grade worsened by 1.1, whereas the non-injected knees changed by only 0.6 grade. Using

Table 2. Radiologic grades of knee X-rays.	
Grade	**Grade of Degeneration**
0:	normal joint
1:	osteophytes, osteosclerosis
2:	narrowing of joint space (< 3mm)
3:	obliteration of joint or subluxation
4:	bone defect (< 5mm)
5:	bone defect (> 5mm)

a paired t-test ratio, these results were statistically significant. In both groups, the clinical evaluation was performed at follow-up according to the knee rating system given in the

Table 3. Radiologic grades of knees at initial visit and follow-up. Knees injected with intraarticular steroids (top graphs) deteriorated at a rate twice that of non-injected knees (bottom graphs).

ADVANCEMENT OF DEGENERATION RATED BY RADIOLOGICAL GRADE IN CORTICOSTERIOD INJECTED KNEES
Group A: Injected Knees   Degeneration advanced in 11 of 14 knees (78.6%)

ADVANCEMENT OF DEGENERATION RATED BY RADIOLOGICAL GRADE FOR NON-INJECTED KNEES
Group B: Non-injected Knees   Degeneration advanced in 43 of 82 knees (52.4%)

Assessment Criteria for the Evaluation on Osteoarthritis of the Knee issued by the Japanese Orthopaedic Association. The criteria is composed of four items, including pain on walking, pain on ascending or descending stairs, range of motion, and joint effusion with a maximum score of 100 for a normal knee. (*See Table 4.*) The average score at follow-up was 69 in the corticosteroid-injected knees and 91 in those not treated with corticosteroid injections. The researchers confirmed that not only do corticosteroids injected into human osteoarthritic knees accelerate articular cartilage degeneration as confirmed by X-ray studies, but they deteriorate joint function compared to non-injected knees.

> **The researchers confirmed that not only do corticosteroids injected into human osteoarthritic knees accelerate articular cartilage degeneration as confirmed by X-ray studies, but they deteriorate joint function compared to non-injected knees.**

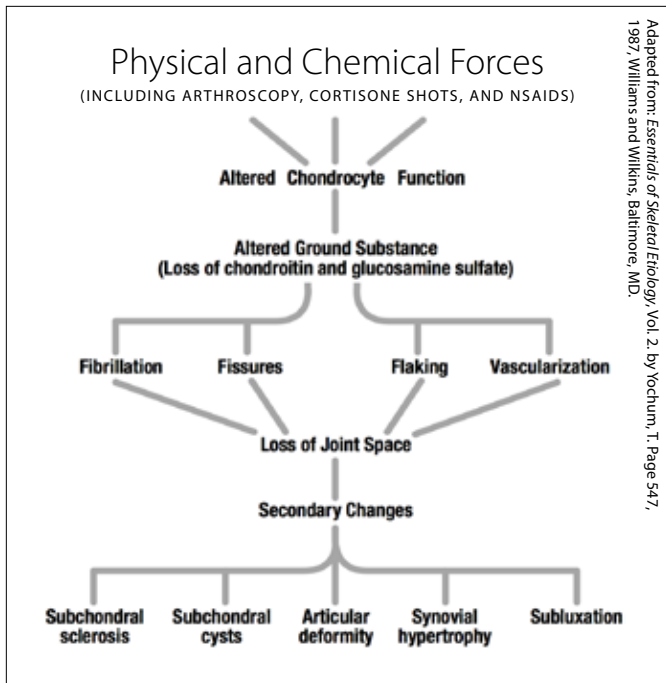### CORTICOSTEROID INHIBITION OF HUMAN ARTICULAR CARTILAGE BIOSYNTHESIS

An early event in the development of osteoarthritis in a joint is proteoglycan loss from articular cartilage.[86,87] Proteoglycans are very large molecules consisting of proteins with attached chains of polysaccharides called glycosaminoglycans. With the exception of hyaluronic acid, glycosaminoglycan units are sulfated, and consequently, highly negatively charged, allowing attraction and binding of water. Because of their great attraction for water, proteoglycans are viscous making them ideal for lubricating fluid in joints. The charges repel each other, which gives them an open structure and is space-filling. These biochemical traits contribute to the mechanical properties of proteoglycans in articular cartilage, such as absorption and distribution of compressive weight, and protect structures in the joints from mechanical damage. Therefore, any decrease in the tissue concentration of proteoglycans, compromises the functional properties of cartilage. Depletion of proteoglycans can result in fibrillation and degeneration of the articular cartilage.[88-90] In all but severe cases of osteoarthritis, the chondrocyte

Table 4. Assessment criteria for the evaluation on osteoarthritis of the knee.

From The Committee for Assessment Criteria on Knee Diseases and their Treatments of the Japanese Orthopaedic Association.

Pain on walking	Points
Walking 1km or more usually with no pain but without regard to mild pain rarely felt on some activity	30
Walking 1km or more regardless of pain	25
Walking 500m or more, but less than 1km without regard to pain	20
Walking 100m or more, but less than 500m without regard to pain	15
Walking indoors or more but less than 100m without regard to pain	10
Unable to walk	5
Unable to stand up	0
Pain on ascending or descending	**Points**
No pain	25
Pain but no pain with handrails	20
Pain with handrails, but no pain when step by step	15
Pain when step by step, but no pain when step by step with handrails	10
Pain even when step by step with handrails	5
Unable to ascend or descend	0
Range of motion	**Points**
Squatting	35
Sideways or cross-legged sitting	30
Flexion of arc of motion of 110 degrees or more	25
Flexion of arc of motion of 75 degrees or more	20
Flexion of arc of motion of 35 degrees or more	10
Flexion of arc of motion less than 35 degrees including ankylosis or severe flexion contracture	0
Joint effusion	**Points**
No edema, no swelling	10
Puncture required sometimes	5
Puncture required frequently	0
Total score	**Points**
	100

response to proteoglycan depletion results in an increase in glycosaminoglycan synthesis.[91-93] (*See Figure 11.*)

In vitro studies of various corticosteroids, including dexamethasone, hydrocortisone, and betamethasone, have shown that they inhibit human glycosaminoglycan biosynthsis in a dose dependent manner.[94-97] Ultimately when human articular cartilage is examined microscopically

Figure 11. The development of degenerative joint disease.
The process can be accelerated by arthroscopy, steroid injections, and NSAIDs, the primary tools of most traditional pain physicians.

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Adapted from: *Essentials of Skeletal Etiology,* Vol. 2, by Yochum, T. Page 547, 1987, Williams and Wilkins, Baltimore, MD.

after intraarticular steroid injections, signs of degeneration are present.[98,99] One human study examined the articular cartilage in the tempomandibular joint (TMJ) after two injections with triamcinolone and compared this to tempomandibular joints that did not receive any steroid injections. The researchers performed microscopic analysis examining the fibrous (top), cartilaginous, and subchondral bony layers of the articular cartilage tissue. The author summarized his results this way, "The results of this study revealed higher destruction to all layers of the joints that received intraarticular injection of triamcinolone acetonide, when compared to the group of joints, which received no steroid injections. This finding firmly supports the hypothesis; intraarticular injection of steroids acts in joints suffering from OA as a lytic agent with the potential to produce a pharmacological arthroplasty."[100] The author noted that his study revealed the complete loss of the fibrous layer in the steroid group in 84% of the specimens and that other studies showed a 100% loss.[101,102] He explained it this way, "This is simply because the joints in this investigation received only two injections of steroids, meanwhile the joints in Poswillo's study received six injections of steroids."

INTRAARTICULAR CORTICOSTEROID USAGE IS COMMON

Since its introduction in the early 1950s, the use of corticosteroid compounds by intraarticular injections has become a common practice in orthopedics and sports medicine. (*See Figure 12.*) Prompt and effective reduction of local inflammation occurs after intraarticular injection of corticosteroids. Most of the substances released by the damaged cells to cause inflammation are greatly decreased in quantity. Corticosteroids also inhibit fibroblasts, collagen deposits, and reduce capillary formation, thus limiting the formation of scar tissue. Generally the relief of pain and inflammation is obtained within a few hours after the injection and can last a few days or a few weeks. Because of their pain-relieving effects, corticosteroids are commonly used in both human and veterinary medical practices.

Intraarticular corticosteroids are recommended in several guidelines for the treatment of patients with knee osteoarthritis.[103-105] Rheumatologists in particular when surveyed state that over 95% of them use them at least sometimes and 53% frequently in the treatment of osteoarthritis of the knee and hip.[106, 107]

While most controlled studies have shown that intraarticular corticosteroid injections are superior to placebo injections for osteoarthritis of the knee, the benefit of such injections is short-term generally lasting from one to three weeks.[108-115] (*See Figure 13.*) No improvement in long-term pain or function has been

Oral	Injectable
Cortisone	Aristocort
Decadron	Celestone
Deltasone	Depo-medrol
Dexamethasone	Kenalog
Hydrocortone	
Kenacort	
Medrol	
Methylprednisolone	
Prednisolone	
Prednisone	
Triamcinolone	

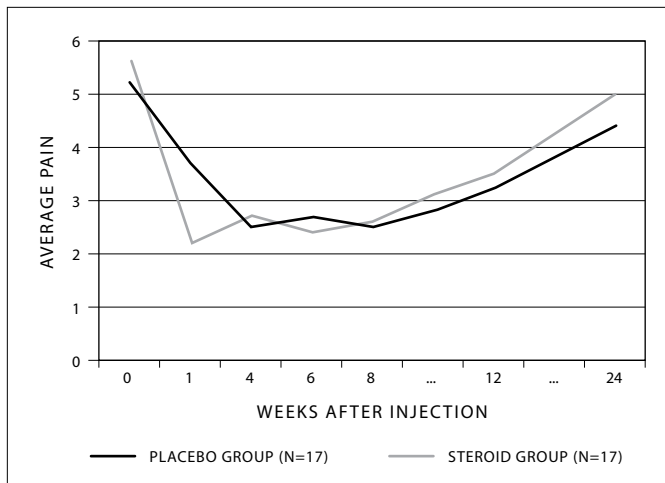**Figure 12. Commonly used corticosteroid medications.**

Figure 13. Average pain score before and at 1, 4, 6, 8, 12, and 24 weeks post-injection, comparing the steroid and placebo groups. As this graph indicates, almost every randomly controlled study shows that steroids have no long term effects in reducing pain compared to placebo injections.

shown by intraarticular corticosteroid injections into the knee. Even systematic reviews summarizing the evidence of intraarticular corticosteroid injections in patients with osteoarthritis of the knee have confirmed that inadequate data exists related to the beneficial use of corticosteroid injections for knee osteoarthritis besides one to three weeks of pain relief.[116-120] In randomized controlled studies of intraarticular corticosteroid injections of other joints including the hip and carpometacarpal joint of the thumb, again short-term results of a few weeks of pain relief was seen, but no long term benefits could be documented.[121-125] One reviewer called the response to intraarticular corticosteroids "brief and transient," noting that the number of potential adverse effects of intraarticular corticosteroids stresses the importance of their judicious use.[126] Another review summarized it nicely, " Local injections of corticosteroids are commonly used in orthopaedic practice on the assumption that they will diminish the pain of inflammation and accelerate healing. Less often considered is the possibility that their use may delay the normal repair response. Unfortunately, there is a paucity of well-controlled studies that provide definitive recommendations for nonrheumatologic use of corticosteroids. Also troubling are the significant potential complications that can occur with their use. The authors believe that use of corticosteroids should be limited to the few conditions that have been proved to be positively influenced by them."[127] In this author's opinion osteoarthritis is not one of them.

GENERAL GUIDELINES FOR INTRARTICULAR CORTICOSTEROID USAGE IN OSTEOARTHRITIS OF A JOINT

The guidelines published by the American College of Rheumatology note, "It is generally recommended, although not well supported by published data, that injection of corticosteroids in a given joint not be performed more than three to four times in a given year because of concern about the possible development of progressive cartilage damage through repeated injection in the weight-bearing joints."[128] The guidelines given by the International Society of Arthroscopy, Knee Surgery & Orthopaedic Sports Medicine state, "Although an extremely useful technique, the intermittent use of intrarticular cortisone should be deployed with caution. The potential risks of provoking hyaline cartilage degeneration, the hazards as they relate to joint infections, and the limitations of cortisone should be fully discussed and disclosed to the patient."[129]

These guidelines are a far cry from what used to be the standard of care. What most patients do not realize is that rheumatologists in the 1950s and 60s used to give ten or more steroid injections per joint per year. Some patients receiving more than 150 steroid injections into their joints.[130]

SUMMARY

From animal studies, corticosteroids have shown to produce a deleterious effect on cartilage metabolism. This is manifested by damage to, and death of, the chondrocytes. The chondrocytes are the cells that synthesize the components of cartilage, mainly the type II collagen and proteoglycans. Because chondrocytes decrease in number and function, collagen and proteoglycan synthesis decline. The net result of these effects is articular cartilage degeneration. The degenerated cartilage loses elasticity, making the joint more stiff. Ultimately, the cartilage thins and there is narrowing of the joint space as evidenced by X-ray. This narrowing is typical of osteoarthritis.

In most of the animal studies, the severe deleterious effects on the joint and articular cartilage, both mechanical and physiological, have been corticosteroid dose-related. Running exercises combined with intraarticular corticosteroids is more detrimental to the articular cartilage than corticosteroids alone. This combination caused a significant enhancement of the loss of chondrocyte cells and matrix compared to corticosteroid injection alone.

In regard to human research, it is an established fact that osteoarthritis and subsequent knee and hip replacements are increasing at an alarming rate. Normal job-related activities, regular exercise and normal aging cannot account for such a dramatic increase. The usual and customary treatment for unresolved pain from an osteoarthritic joint often involves a cortisteroid injection. Because of the ubiquitous use of corticosteroid shots, a direct chondrotoxic effect from corticosteroids could explain this increase. Steroid arthropathy and "charcot-like arthropathy" have been reported in the arthritic human knee and hip joints with the use of intraarticular corticosteroid injections. These changes could also be due to the temporary suppression of pain, which encourages excessive and unguarded activities of diseased joints, resulting in rapid progression of joint destruction. This is especially true of athletes who typically return to full intensity sport activities with a few hours to a few days after a cortisone injection.

The results of human studies revealed a higher destruction of articular cartilage in corticosteroid-injected joints than those who received no injections. Corticosteroid-injected joints show a greater deterioration of all layers of the articular cartilage. Long term this is manifested by more advanced osteoarthritis in the joint leading to a decline in joint function. It is this author's opinion based upon the scientific research that this is one of the main factors that explains the tremendous increase in osteoarthritis of the knee and hip coinciding with the dramatic rise in knee and hip replacements.

CONCLUSION

There is no clear evidence that corticosteroids injected into the osteoarthritic knee, hip, or other joints have long term benefit. Definite evidence exists, however, primarily from animal studies, that corticosteroids are harmful to the articular cartilage. Intraarticular corticosteroid injections result in severe deleterious effects, both mechanical and physiological, on the joint and articular cartilage. Most of these changes are dose-related. The catabolic effects of intraarticular corticosteroids include a massive decrease in the synthesis of all major articular cartilage matrix components. The loss of glycosaminoglycans, proteoglycans, proteins and matrix collagen leads to the ultimate breakdown of the articular cartilage. The net result of corticosteroid joint injections is an acceleration of the osteoarthritic process which is manifested in the

dramatic rise of cases of osteoarthritis of the knee and hip and subsequent joint replacements. Forty years ago, in an Editorial for the British volume of the *Journal of Bone and Joint Surgery*, Sweetnam stated, "We now have evidence, both clinical and experimental, that apart from the well recognized hazard of infection, intraarticular injections of corticosteroids, certainly, if repeated, may be harmful, yet the practice has continued. We believe that it should now cease."[131, 132] This sentiment is reiterated by the International Society of Arthroscopy, Knee Surgery, and Orthopaedic Sports Medicine who state, "Although an extremely useful technique, the intermittent use of intraarticular cortisone should be deployed with caution. The potential risks of provoking hyaline cartilage degeneration, the hazards as they relate to joint infections, and the limitations of cortisone, should be fully discussed and disclosed with the patient."[133, 134]

In summary, intraarticular corticosteroid injections degenerate articular cartilage in osteoarthritis. Studies have shown no long term benefit in joint osteoarthritis and substantial scientific evidence has been offered to the contrary, that the long-term sequelae of injections of corticosteroids into degenerated joints accelerates the arthritic process. Despite its widespread use, substantial scientific evidence exists to dissuade both clinicians and patients from using intraarticular corticosteroids in the treatment of osteoarthritis. The continued use of intraarticular corticosteroid injections in the treatment of osteoarthritic joints is deplorable. ■

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