WONDER WHY?

A SCIENTIFIC EDITORIAL

# The Regeneration of Articular Cartilage with Prolotherapy

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ABSTRACT

*What most people may not realize is that chondrocytes, the cells that make articular cartilage, are metabolically active. Chondrocytes proliferate and actively make articular cartilage. Osteoarthritis is an example of this, in that both the degradation and synthesis of articular cartilage are enhanced. It is well known that in osteoarthritis, chondrocytes retain their proliferative activity. Osteophytes or bone spurs are an example of this activity.*

*Another example of adult articular cartilage cells' replication is acromegaly. In this condition the body produces an excessive amount of human growth hormone and with it, articular cartilage. Acromegalics often suffer from joint abnormalities caused by proliferation of chondroytes in articular cartilage. In other words, they produce too much cartilage.*

*When a healthy articular cartilage cell is injured, it demonstrates an enhanced reparative response and can replicate its DNA to form new cells. The rate of formation of articular cartilage can be enhanced by such stimuli as altered hydrostatic pressure, varied oxygen tension, growth factors, as well as nutrient and substrate manipulation.*

*If by traditional orthopedic surgery or medical standards, articular cartilage injury or degeneration causes such symptoms as knee pain, stiffness, clicking, crunching, and inability to walk, then the reversal of such symptoms with Prolotherapy must mean that articular cartilage regeneration has taken place. In this scientific editorial, the author makes the case for using Prolotherapy as the treatment of choice for degenerated joints.*

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Simply put, I believe that articular cartilage is regenerated with Prolotherapy. In my opinion, Prolotherapy should be the treatment of choice for most cases of pain involving the degeneration of a joint. It is common knowledge that even the most effective current treatments for osteoarthritis do not restore the joint. Conservative treatments such as exercise, medications, physical therapy, and lifestyle modification can decrease symptoms and improve mobility, but they do not reverse the disease. I believe if Prolotherapy were utilized to its fullest in the treatment of knee, shoulder, and other peripheral joint degenerative conditions, it would be shown to be the one treatment that does restore some, or most, of the degenerated structures, as well as the functions of the joint.

What most people may not realize is that chondrocytes, the cells that make articular cartilage, are metabolically active.[1] Yes, chondrocytes do proliferate and actively make articular cartilage. In normal cartilage, there is a strict regulation of cartilage turnover, a delicate balance between synthesis and degradation. The problem is, for those suffering from osteoarthritis, the system is imbalanced. There is more cartilage degeneration than rebuilding.

In osteoarthritis, both degradation and synthesis of articular cartilage are enhanced. The problem is that the "messenger" molecules that allow cells to communicate and alter one another's functions, called cytokines, cause more breakdown of articular cartilage than repair. The catabolic (break down) cytokines IL-1, TNF-*a*, IL-17, and IL-18 act to decrease extracellular matrix synthesis (cartilage synthesis). The anabolic cytokines (substances that build up) IGF-1, TGF-*B*1, 2, and 3, fibroblast growth factors (FGFs) 2, 4, and 8, and the bone morphogenetic proteins act to stimulate extracellular matrix synthesis.[2,3] In osteoarthritis, unfortunately, the catabolic cytokines are winning.

| CATABOLIC CYTOKINES | ANABOLIC CYTOKINES |
|---|---|
| IL-1 | IGF-1 |
| TNF-α | TGF-β1, 2, 3 |
| IL-17 | FGF-2, 4, 6 |
| IL-18 | |

**Physiology of osteoarthritis.** While articular cartilage is stimulated in osteoarthritis, the net result is degeneration in part because of the increase in catabolic cytokines. One of Prolotherapy's effects on the physiology of osteoarthritis is thought to be an enhancement of anabolic cytokines which stimulate cartilage regeneration.

It is well known that in osteoarthritis, chondrocytes retain their proliferative activity.[4,5,6] As a matter of fact, a number of biochemical studies have demonstrated enhanced synthesis of the extracellular matrix of cartilage.[7,8] Chondrocytes attempt to repair the damaged matrix in osteoarthritis by increasing their anabolic activity.[9,10] One of the reasons for this is that on a molecular level, a significant proportion of adult articular chondrocytes start to re-express a chonodroprogenitor phenotype in osteoarthritic cartilage degeneration, which is comparable to the chondroprogenitor phenotype observed in fetal skeletal development.[11,12] In other words, with injury/degeneration, the adult chondrocyte cells change to more "primitive" cells, which have more proliferative ability. In the natural history of the disease, despite this increased activity, a net loss of proteoglycan content (extracellular cartilage matrix) is one of the common features of all stages of osteoarthritic cartilage degeneration.[13]

One of the main hallmarks of osteoarthritis in a joint is the development of prominent osteochondral nodules known as osteophytes. These are also called osteochondrophytes or chondro-osteophytes. Most of us know them as bone spurs. Indeed, the presence of osteophytes in a joint, more than any other pathological feature, distinguishes osteoarthritis from other arthritides.[14] *Osteophytes are an example of new cartilage and bone development* in osteoarthritc joints, and arise from tissue associated with the chondro-synovial junction or from progenitor cells residing in the perichondrium.[15,16] This basically means there is a population of joint cells (pluri-potential cells) that can respond to injury and differentiate into cells that make cartilage and bone. The purpose of osteophytes is presumed to be the stabilization of joints affected by osteoarthritis.[17]

**Adults with Acromegaly have the problem of too much cartilage.**

When larger osteophytes are examined from human patients, areas of hyaline cartilage can be seen to extend to the surface of the osteophyte. These cartilaginous tissues resemble genuine articular cartilage in chondrocyte morphology and in extracellular matrix. Interestingly, the anabolic factors TGF-B and TGF-B2 have been found in osteophytes from human femoral heads.[18] Again this signifies that adult articular cartilage retains repair (anabolic) activity.

## INCREASED ARTICULAR CARTILAGE THICKNESS IN ACROMEGALY

One of the major problems in osteoarthritis care today is traditional medicine's inability to promote effective cartilage regeneration in the presence of adult chondromalacia (cartilage degeneration). **Yet such regeneration is consistently present in acromegalics.** Acromegaly is a condition whereby the pituitary gland secretes too much human growth hormone (HGH). It is a disease characterized by the gradual enlargement of the bones of the hands, feet, head and chest, and thickening of the skin, lips and vocal cords. What is also characteristic of this condition is that there is an excessive amount of articular cartilage in both weight-bearing (knees) and non-weight-bearing joints.[19] Acromegalics often suffer from joint abnormalities caused by the proliferation of chondrocytes in articular cartilage. Since this condition typically occurs after puberty, the increased human growth hormone secretion in acromegaly somehow, either directly or indirectly, stimulates adult chondrocytes (cartilage cells) to make cartilage. People with acromegaly have tremendously thick articular cartilage, which can be diminished by decreasing their HGH secretion.[20]

HGH is known to cause the liver to increase production of Insulin-like growth factor-1 (IGF-1). Circulating and locally produced IGF-1 is known to stimulate DNA synthesis, cell replication, and proteoglycan and glycosaminoglycan synthesis in articular chondrocytes.[21] IGF-1 and HGH have both been shown to stimulate the growth and repair of adult articular cartilage.[22,23,24] One reason for this cartilage growth can be that some cartilage cells have HGH receptors.[25]

## MORE EVIDENCE OF ARTICULAR CARTILAGE REGENERATION

What happens to articular cartilage when it is subjected to mechanical trauma? It is important to consider the main issue. Can adult articular cartilage respond to appropriate stimuli by an increase in its synthetic activities for DNA and matrix components? In other words, can chondrocytes replicate and make cartilage? Central to this discussion is the consideration of the ability of any tissue to increase its rate of DNA and protein synthesis. Regardless of the tissue involved, the process of repair is a cellular one in the sense that fibroblasts, or specific cells (osteoblasts, chondrocytes for example), must synthesize the repair material. For the most part, these are "new" cells that evolve by cell replication and modulation of existing cells, or from cells that have migrated either from the margins of the wound or from blood vessels entering the tissue. It is therefore important to recognize that DNA replication and cell division are essential characteristics of any repair process.

The confusion in regard to articular cartilage repair stems from the fact that chondrocytes from immature cartilage are capable of dramatic repair and synthesis, whereas aging chondrocytes show much lower rates of cell replication.[26,27] This is where the notion of "cartilage cells don't replicate" stems from. The problem with this logic is that a normal adult chondrocyte is phenotypically different from an injured chondrocyte. Analysis of cartilage from joints with osteoarthritis has demonstrated, over and over again, an increased number of cells in clones and evidence for DNA synthesis by a number of means including 3H-thymidine metabolic studies, autoradiography, and even histological demonstration of mitotic figures.[28,29,30] These data suggest that under circumstances of chronic injury, such as is seen in osteoarthritis or trauma, chondrocytes are capable of mounting a significant reparative response and can replicate their DNA to form new cells.[31] This is fact. Chondrocytes can divide, and do so in the adult animal/human with osteoarthritis and from other stimuli. Ample evidence now exists that articular chondrocytes from immature and adult animals can vary the rate at which they make cartilage matrix necessary for repair. This rate of proteoglycan synthesis can change in response to such diverse physical and pathological states as osteoarthritis (as discussed), altered hydrostatic pressure, varied oxygen tension, alternations in pH, calcium concentration, substrate concentration, and the presence of growth hormone (as discussed), growth factors, ascorbate, vitamin E, and so on.[32,33,34,35,36] I could easily elaborate on each of these, but the reader is encouraged to check the references for further information. Therefore, it is reasonable to conclude from the above that injured adult articular cartilage chondrocytes have the capacity to substantially increase their rate of matrix synthesis, and that the possibility exists of chondrocyte participation in the repair of articular cartilage. All that is really needed is a method to stimulate that repair maximally. This is where Prolotherapy fits in.

**Cartilage repair can be stimulated by a number of means: pressure changes, trauma, varied oxygen, tension, pH alterations, calcium, growth hormone factors, vitamins, nutrients.**

## PROLOTHERAPY: THE TREATMENT OF CHOICE FOR DEGENERATED JOINTS

George S. Hackett, MD coined the term Prolotherapy. As he describes it, "To the treatment of proliferating new cells, I have applied the name *Prolotherapy* from the word *prolix* (Latin), meaning offspring; *proliferate*-to produce new cells in rapid succession. My definition of Prolotherapy as applied medically in the treatment of skeletal disability is 'the rehabilitation of an incompetent structure by the generation of new cellular tissue.'"[37] While traditionally used for ligament and tendon repair, Prolotherapy has a long history of being used for degenerative joint disease.[38,39,40,41] Like the chronic knee pain study published in February 2009 issue of the *Journal of Prolotherapy*,[42] Prolotherapy has remarkable pain-relieving effects. But when a person with degenerative knee arthritis reports less stiffness and crunching in the knee, as well as improved motion, are we to assume that there has been cartilage repair? I would answer the question with an emphatic "yes" in most cases. But some would remain skeptical. This is why the February 2009 issue of the *Journal of Prolotherapy* also presented five before and after X-rays of knees showing cartilage regeneration.[43] Does this prove that all Prolotherapy treatments on degenerated knees stimulate cartilage regeneration? Absolutely not! But it

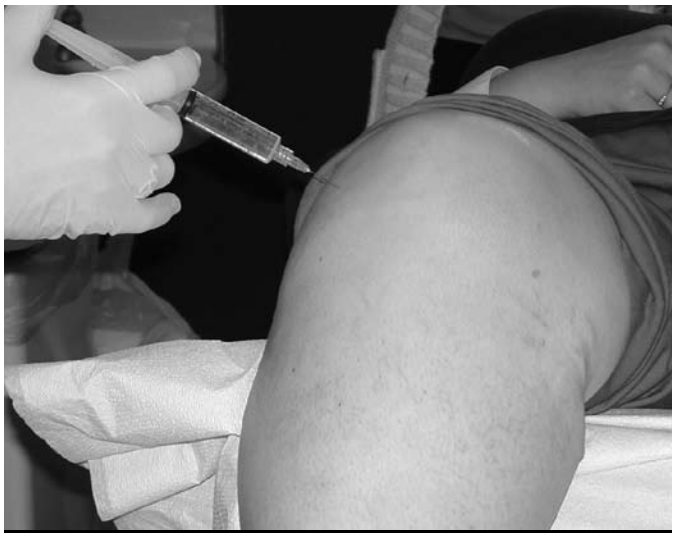
surely shows that Prolotherapy treatments to human knees do have the potential to regenerate articular cartilage. For those who have had numerous treatments and have seen the function, signs, and symptoms of their degenerated joints reverse with Prolotherapy, is it reasonable to assume that the articular cartilage is being stimulated to repair? How else would you explain a decline in stiffness, clicking, and crunching in the person's knee treated with Prolotherapy? How do you explain the inability to walk or do any athletics, but yet with a number of Prolotherapy injections into and around the knee, the person regains his walking ability and is now able to perform athletics? How about improvement with Prolotherapy in those patients who have been told they need knee replacements, or those whose doctors say there is no other treatment available for them? What about in these cases? If the person receives Prolotherapy to their end-stage osteoarthritic joint and not only do they *not* need a knee replacement, they are back to dancing, how do you explain it? Placebo? I think not. Something has changed. Their joint architecture has changed. There has been some rebuilding inside their joints. In essence, they have a regenerated joint. The chondrocytes have been activated to start making cartilage and that cartilage has been laid down.

**Evidence of cartilage repair after Prolotherapy: Positive changes on X-ray, less clicking in the joint, less grinding, less pain, smooth gliding joint.**

I believe in changed lives. I believe a changed life is enough. In other words, if a person cannot walk much because of a degenerated knee and has been told by an orthopedist that he needs a knee replacement, but he refuses and decides instead to get Prolotherapy, and if after Prolotherapy treatments he can walk well with virtually no symptoms, I am satisfied. Their life was changed with Prolotherapy. I believe the patients when they tell me that it was the Prolotherapy that turned their lives around. I believe that the Prolotherapy regenerated the injured tissues. I believe that the person can now have a full life. That full life is because of Prolotherapy. Prolotherapy worked for them. I do not need an MRI or X-rays or a biopsy of cartilage cells to know that Prolotherapy worked!

The bottom line is you can't have it both ways. If the orthopedist is saying to a patient that your knee pain, grinding, crunching, pain upon bending your knee, and your inability to walk without a limp is from your cartilage degeneration and you need a knee replacement, then the opposite must also be true. If that same patient, after receiving Prolotherapy to the knee, has no more, or very little, pain, grinding, etc., can walk unlimited and does hiking and climbing, then it must mean that their degenerated cartilage has been *regenerated!* To put it bluntly, Prolotherapy regenerated their cartilage! This is my main point!

I know there are a lot of skeptics out there. They want "evidence" that Prolotherapy works. They need to see before and after X-rays and MRIs. Well, that is part of the purpose of the *Journal of Prolotherapy*. The goal is to educate the world on the life-changing effects of Prolotherapy. Some of the people in the world who need educating are the traditional doctors who treat pain patients. They need to know of the life-changing effects of Prolotherapy on degenerated joints. One of the effects of Prolotherapy is to change a degenerated joint without much cartilage to a joint that has more cartilage. How will that appear to the physician examining the joint? The doctor would notice a smooth-gliding joint instead of a joint that makes grinding, clicking, and popping sounds while the physician puts the joint through its range of motion. It is definitely noticeable and demonstrable. To the patient, the joint after Prolotherapy will produce much less crunching or clicking sounds when



**Prolotherapy of the knee.** The knee is the most common joint treated with Prolotherapy for articular cartilage regeneration.

the knee or joint is moved, as well as when going up and down stairs. As a given, he will experience less pain and stiffness.

## CALL TO ACTION

Here are some suggestions to those with degenerated joints that were regenerated with Prolotherapy, and for those who use Prolotherapy in their practices. Let's start obtaining before and after Prolotherapy X-rays, and if possible even MRIs. Make sure the X-rays and MRIs taken after Prolotherapy are compared to the ones taken before Prolotherapy, and are evaluated by an independent radiologist who understands that the patient had Prolotherapy. I believe that you will most likely see structures be regenerated! The average radiologist has never seen menisci or cartilage tissue regeneration. Tell him you performed (or received if you are the patient) Prolotherapy on the joint. Ask him specifically if he sees regeneration of articular cartilage, menisci, ligaments and any other structures? Do not be surprised when the radiologist says, "yes." Send us the films to be published in the *Journal of Prolotherapy*. Perhaps then we can eliminate some of the skepticism about Prolotherapy and people can receive the treatments they really need, such as Prolotherapy. At least one of the myths that prevails in the world of orthopedics, that articular cartilage does not regenerate, will be dismissed once and for all. We can then rejoice because people with pain will get the treatments they need. Perhaps people everywhere will finally understand that cartilage can be stimulated to repair, and that it is Prolotherapy that is needed to regenerate articular cartilage. ■

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