Acta Scientific Orthopaedics (ISSN: 2581-8635)

Volume 6 Issue 8 August 2023

Conceptual Paper

# Arthrosis and Visco supplementation Frare

**André Luiz***

*Regenerative Medicine Department, Brazilian Society of Pain, Brazil*

***Corresponding Author:** André Luiz, Regenerative Medicine Department, Brazilian Society of Pain, Brazil.

**Received:** May 22, 2023

**Published:** July 09, 2023



Arthrosis is prevalent in approximately 25% of adult individuals, and is the greatest cause of morbidity and restriction in individuals over 40 years of age, and the number of people who suffer from this disease is very high throughout the world.

It is the most common joint disease, presenting not only pain, but heat, stiffness, crepitus, instability, and usually begins without pain.

It can be of primary or secondary origin.

The primary is genetic, mechanical errors, systemic inflammation, and calcium deposition. The secondary is usually traumatic (mechanical trauma, overuse, obesity).

It is a disease of the joint as a whole, affecting not only the cartilage, but the synovium, and also the subchondral bone. It is asymptomatic temporarily, but will always become symptomatic and will always evolve.

The cartilage has a cell that produces its chondral matrix, which is the chondrocyte, and the chondrocyte lives well in a hypoxic environment, it doesn't react well to high oxygen pressure, and as in arthrosis new vessels are created that will penetrate the cartilage, they will modify this environment, making it more prone to high oxygen pressure. So this is where the vicious process of cartilage degradation begins.

Cartilage is composed of 70% water, also type 2 collagen, aggrecanes, and proteoglycans. Chondrocytes can detect mechanical stress, through their receptors, and this maintains homeostasis, or worsens homeostasis, with excessive loads. This causes the internal environment of the joint to lose its proteoglycans, which are the natural protectors of cartilage.

We have a type 2 collagen network in the regions, close to the subchondral bone, that are not degraded, because they are coated with proteoglycans. Where there are proteoglycans, cartilage is not degraded, so viscosupplementation is important, because the hyaluronic acid viscosupplement will protect the cellular matrix and prevent the degradation of proteoglycans.

The expression of metalloproteinases 1 and 13 are very specific for the destruction of type 2 collagen. But with time, there is a depletion of these proteoglycans. The proteoglycans have the function of protecting type 2 collagen.

But with overload and inflammation, that's when the degradation of the cartilage begins, and catabolic factors associated with this disease are released, mainly prostaglandin E2, where there will be a very large interaction of release and increased expression of meatolproteinases, and this can lead to a depletion of proteoglycans.

So in osteoarthritis, we have a gradual disappearance of cartilage, we have the loss of chondrocytes, we have the formation of clusters, with hypertrophic chondrocytes that can't make the necessary type 2 collagen deposition.

In the knee and also in the hip, we have a joint fat called FAT PAD, and the fat pad in patients with arthrosis, change its configuration, becoming inflamed, and start the release of adipokines, and there is also a neo-inervation and neo-vascularization that generate pain, and it can keep the low-grade inflammatory process within the joint, locally, but on the other hand, the fat pad is the best source of stem cells for knee treatment.

But what happens to the cartilage if it was actually made to receive load? We have some determinants, if this cartilage, will live a little or a lot. So aging is a big problem, metabolic syndromes, traumas, and activation of cartilage inflammation cause it to degenerate faster.

About aging, the chondrocyte from the moment it has been submitted to a low-grade inflammatory process, in this mechanism, there is an increase in the senescence of the chondrocyte in the cellular matrix.

Still on aging, we have to pay a lot of attention to this, we have to pay attention to the senescence mainly due to the expression of beta galactamase, even if we can improve the quality of the chondrocytes, these chondrocytes already have a shorter telomere, this leads us to think, if this is adequate to use this type of chondrocyte for transplantation or even in the placement of membranes in articular defects. It's already an aging chondrocyte. Not being a viable option.

What we have to understand is that in arthrosis, we have a problem that is cellular. And what seems to be very important is the mitochondria. The mitochondria play a very important role in arthrosis, because depending on the activation via KASPASE of cytochrome C, the cell can die. In the inflammatory process we also have an increased expression of hydrogen peroxide, and this causes an oxidation that destroys the tissue.

AMPk controls the mitochondrial dynamics, and is a key to catabolism in arthrosis. We also have mitochondrial DNA, which in models with altered homeostasis, will be carried even outside the mitochondria, outside the cell, leading to inflammatory environments, and we have here a destructuring of the Krebs cycle.

The Krebs cycle is fundamental for the survival of the cell, and we know that in arthrosis we have an alteration of this Krebs cycle leading to a cell with a more anaerobic energy production, spending a lot of energy, and producing little efficiency. Even the joint likes little interaction with oxygen.

In addition, we have to think that arthrosis will almost invariably cause an altered and increased production of crystals, which cause many problems with deposits. We need ATP for cellular energy, and this cellular energy will happen from the moment that we have the input of phosphate in the mitochondria, for this transformation. Each ATP molecule will generate two molecules of phosphate and in the cell membrane we have two important receptors, one is the ankylose receptor and the other is the alkaline phosphatase receptor, which are important in the production of the dephosphorylation of inorganic pyrophosphate, and the organism needs to dephosphorylate this molecule so that it again enters this cycle, and is transformed intra-cellularly, and when this doesn't happen, more crystal deposits start to form. The hydroxyapatite crystals are produced by basic calcium phosphate. When the process of removing the phosphate groups does not happen properly.

Also, we know that we have several families of enzymes in the chondrocytes, which are able to convert ATP into other nucleosides that convert into inorganic pyrophosphate. And another enzyme pyrophosphate that is involved in this phosphorylation, which is converted to AMP, and with increasing calcium saturation, we form the crystals of CCPPD or in the other pathway mainly with altered magnesium metabolism, we can form, the BCP. Which are two crystals.

The calcium pyrophosphate and the hydroxyapatite, which are deposited in the cartilage, and on the magnesium metabolism.

In the formation of BCP, when it is deposited in the cartilage, which is an apatite, it immediately does a much smaller induction of interleukin B and tumor necrotizing factor, via monocytes, than that of GOTA, and than monosodium urate. It increases the concentration of prostaglandins, and idiopathic deposition can occur as in tumor calcinosis, and ligament calcification, so it is a disease that can reach beyond the cartilage, and far beyond the joint.

In calcium pyrophosphate, which is also a crystal and has several similarities with BCP, it is oncogenic and mitogenic, it increases the production of proteinases, which causes joint degeneration, mainly by the expression of interleukin 8, which is an attractive chemical for the neutrophil, and it inhibits neutrophil apoptosis, and the neutrophil should live only 24 hours, it becomes a cowardice against cartilage, and this generates chronic inflammation and crystal rupture.

The deposition of calcium pyrophosphate is what we see in the X-ray and in the MRI the outlines or double line. There is also chondrocalcinosis, which is a disease that can have some associations, such as hemochromatosis, primary and secondary hyperparathyroidism, and hypomagnesemia. So magnesium increases the solubility of calcium pyrophosphate crystals. So magnesium supplementation must be done, for a magnesium control mechanism.

In acute treatment the goal is to improve the quality of the joint at the time.

And in chronic arthrosis to treat the causes, in addition to treating the progression of the disease.

The asymptomatic patient requires no treatment, none decrease the crystals, Alupurinol can reduce calcium urate, not calcium pyrophosphate.

Hyaluronic acid is the good choice as it inhibits interleukin 8.

The gout crystal, has a very large interaction in arthrosis, one causes the other, and it is a very prevalent disease. In other words, the gouty ones become atrophic, and the arthrosic ones become gouty.

We always have to think that the purine metabolism, which will cause the increased synthesis of uric acid, is a genetic overproduction, a direct conversion of glycine into uric acid, mainly due to the deficiency of hypoxanthine (enzyme). So, analyzing these cases, in the treatment of arthrosis, we have to evaluate the kidney and liver function, and try to improve these factors whenever possible.

The prevalence of arthrosis is higher in the hand, but is more symptomatic in the hip and knee, there are structural factors that are important, the chondrocytes will suffer hypertrophy, and will become a worse or less functional chondrocyte, and the alteration of the subchondral bone is so much more important than the degradation of the cartilage itself. And the main treatment already studied and with several positive scientific studies in its favor is the use of Platelet Rich Plasma (PRP).

There is a very large association between hand arthrosis and obesity, and this shows that obesity not only increases the weight on the joints, but also causes chronic inflammation, especially the release of adipokines, which destroy joints that are not load-bearing, and that is why the reduction in body weight and exercise improve the quality of life of patients with arthrosis. We always include in the treatments the use of medications that help reduce adipocytes and their deposition in the central abdominal region.

And one thing that is becoming more and more evident is that the mortality rate of patients with arthrosis is much higher than that of patients without arthrosis, due to the limiting factors, the lack of mobility and a good understanding of the pathological mechanism of the disease, which causes patients to have more metabolic problems than non-arthrosis patients. And everything we do in the treatments is to get the patient back to exercising, and to have more independence every day.

Another thing that we have to think about in arthrosis is peri-articular lesions and osteophytes, which are mainly caused by growth factors. The edema of the subchondral bone (of the bone marrow), which is directly related to the HANK receptors, generates a negative homeostasis of the subchondral bone, thus having more osteoclast formation, and a reduction of osteoblasts, leading to a fibrosis of the subchondral bone.

Another factor is that formerly we had this model that the synovium only started the inflammation process after a cartilage fragment reached it, but today we know that just the increased production of interleukins can already lead to synovitis.

The inflammasome, is released all the time, mainly due to the kaspase 1 cascade, this is a nuclear reaction, that today we have strategies to control and prevent this vicious cycle of inflammation via synovitis, through the use of infiltration with hyaluronic acid and platelet-rich plasma.

Obesity will also increase the expression of adipokines, and we have several mechanisms of cartilage destruction, inflammation of the synovia, caused by excessive fat accumulation, especially in the abdominal region.

The mechanics of each joint is very individualized. Stabilization is very important, so the mechanisms must be controlled with exercises. A classic example is ACL rupture, increasing the contact area of the cartilage, and increasing the incidence of arthrosis in these patients.

The problem is that surgery only solves the ACL injury, and some papers bring us some surprises, which is an example of a study from the American Journal of Sports Medicine "Prevalence of Tibiofemoral osteoarthritis 15 years after nonoperative treatment of anterior cruciate ligament injury", which did 15 years after patients who did not operate on the ACL, all patients X-rayed, and 16% had arthrosis in 15 years, patients without ACL surgery and without meniscal injury had no arthrosis, and patients with ACL injury and meniscal injury 40% had arthrosis, and patients who reconstructed the ACL 35% had arthrosis. And the patients with ACL and meniscal injury who had surgery 46% of the patients had arthrosis. And this leads us to think that the concepts of being obliged to do ACL in order not to have arthrosis in the future has fallen by the wayside.

We already know that mechanics can be the hero or the villain of cartilage degeneration, so low frequency stimulation of cartilage, leading to a small piezoelectric effect, does not cause any cellular response, when it is medium it works anabolically, and when it is above a threshold of 10% it is catabolic. Using cartilage is good for anabolism, but with a good measure of charge. Not using it will not cause anabolic effect, and if you use too much it will generate catabolic effect.

Another example is the dissociation between imaging and the clinic; it is known that prosthesis are not to be performed, because

the X-ray is not good, but the patient has to have clinical signs of failure in conservative treatments, in order to indicate arthroplasty. The image is not operated on.

About the treatment, we should make it clear that it is not only the Hyaluronic Acid that is important, Lubricin also has its degree of importance, it does a bioregulation of the cytokines growth factors, and besides that we have some resident macrophages, It camouflages the chondral lesion, not allowing the neutrophil to be attracted, and also to prevent the degranulation of neutrophils by chemotaxis of other neutrophils. When this system is exhausted, the neutrophils quickly go into action and destroy the cartilage.

The synovial tissue, it has to be remodeled, it is not an epithelium, but anyway, in this revitalization process, we have something very similar to these transitions of mesenchymal epithelium, and other mesenchymal epithelial transitions. There are these transformations to try the process of restoration of the synovium.

The genetic factor is very important, in more or less 60% of arthroses, are of genetic origin, and generally these genetic origins are not only arthrosis, but also associated genetic diseases, mainly crystal formation, central adiposity, and metabolic errors.

Hyaluronic acid has a great capacity for synovial protection; however, we must always look at subchondral edema, and if it is present, we have to associate hyaluronic acid with PRP, in order to reduce subchondral edema and thus preserve the chondral lesion from occurring again.

An article published in 2020, "is the association of hyaluronic acid and PRP for treating severe type IV arthrosis worth it?" Two groups of patients were taken, one group with moderate arthrosis and one with more severe arthrosis. Both groups had weekly injections of HA and PRP, although the group with more severe arthrosis was older, it was noticed that the improvement in pain and function was equal and similar in both groups. So the answer is the more severe arthrosis is very worthwhile, mathematical and analytical answer. It can delay the indication of prosthesis in patients.

The evidence for hyaluronic acid in arthrosis is getting stronger every day, since conventional anti-inflammatory drugs only accelerate the arthrosis process, and several studies show this.

In cartilage degeneration we only have one opportunity, and that is when the cartilage edema starts, without the destructuring of the collagen system, and even more so when the patient has no pain, and it is precisely in these cases, where edema is installed, that we need to perform the arthrocentesis procedure, to prevent the neutrophils from destroying the resident cartilage, because when the collagen system ruptures, there is no cure, we can only delay arthrosis and arthroplasty.

This is called preventive medicine to be able to cure arthrosis.

What happens when we don't manage to delay arthrosis is a severe alteration of the collagen, a depletion of proteoglycans, increasing chondroitin sulfate and decreasing our Gag's, and we're going to have an increase in metalloproteinases, and we're going to have initially an increase in edema, and then a decrease in water as we lose cartilage, and we're going to have a decrease not only in the concentration of HA but also a decrease in the molecular weight of the hyaluronic acid (HA) molecule.

The three components of arthrosis are: inflammatory, mechanical, and neurogenic. Let's look at how HA behaves in these three factors.

Synovial fluid has an alkaline pH, and it protects the cartilage, inhibits the loss of proteoglycans, and inhibits the proliferation of inflammatory cells in the joint.

We have known since 1966 that there is a decrease in the size, amount, and molecular weight of HA with age and with the onset of arthrosis, and the use of corticoids reduces the synthesis of endogenous HA, and when corticoids must be used, always use them in the short term and for the shortest time possible, because in the long term they damage the cartilage.

The leukocytes do exactly the activation of phagocytosis, release lysosomal enzymes, generate reaction to oxygen, and destroy cartilage. And we already know that HA can inhibit leukocyte movement. As the concentration of HA increases, the leukocytes move less. So much so that at 4mg/ml of HA there is an inhibition of leukocyte lysosymes, while at 1mg/ml there is no inhibition.

The synovial fluid is important from the mechanical point of view, for its rheological effects, so the HA in the synovial fluid has a characteristic that has a dilating effect, which saves energy for the joint, for example during a run, the synovial fluid reduces the pressure of the joint mechanics. In inflammatory fluid it makes a pseudo-plastic curve.

The main properties for the rheological effect are HA and Lubricin, Albumin, Globulin, and Fibrinogen, but the main ones are HA and Lubricin.

In work with cadavers, the coefficient of friction was measured, and when we took out HA and Lubricin the coefficient of friction was very high, and the lowest coefficient is in the association of the two.

HA is a high molecular weight polysaccharide in the various tissues we encounter. It absorbs impact, it acts as a lubricant. And we have a normal synovial fluid concentration of 3-4mg/ml of HA and the molecular weight is 5 million daltons.

So in arthrosis, we have an alteration of the homeostasis, increased interleukins and tumor necrotizing factor.

HA is pro-inflammatory and anti-inflammatory, but it depends on the size of the molecule.

The low molecular weight ones below 1mDa interact with cd44 and Twin like receptors, blocking these receptors, and causing a pro-inflammatory nuclear reaction.

And the high molecular weight ones, they interact with CD44, with the Rans, and will inhibit the interleukin1 receptor, and cause an anti-inflammatory nuclear reaction.

In synovitis from the moment that we have the interaction of interleukin 1 in the receptor, we have a cellular transcription, for nuclear, when we get to the MAC's, the protein kinases, we know that if they are not phosphorylated, they will not have a nuclear internalization. They internalize in the nucleus and increase the interleukins.

When we use HA, the interleukins interact at the CD44 receptor and at icam, they do a suppression of the phosphorylation of the protein kinases, and they can't do a nuclear interaction, and they can't do an experimentation of the interleukins.

In the chondrocyte it's more or less the same thing, from the increase of phosphorylation of protein kinases, we have nuclear internalization, and expression of interleukins and metalloproteins, HA prevents phosphorylation, not letting the expression of metalloproteinases happen.

As for the tumor necrotizing factor, the process is slower, the protein kinases will need phosphorylation to go to the nucleus. And HA does not go directly into the cytoplasm to prevent phosphorylation, it first intervenes in the nucleus by reducing MPK5, and it is this that reduces the expression of the metalloproteinases.

Hyaluronic acid has two roles, physiological-mechanical and biomechanical. And then through it we get interaction with the cartilage, with the synovia, and with the synovial fluid, forming an endogenous synovial fluid, improving chronic inflammation of the synovia, and improving the homeostasis of the cartilage, improving pain and function.

Extremely safe, and with no side effects.

AH of bacterial fermentation origin (synthetic) is far more superior, than that of animal origin (rooster crest).

CD44, is the main receptor in mediating the proliferation of the chondrocyte concentration, and it receives the HA in the chondrocyte.

HA improves pain, and provides analgesia immediately from the moment the joint received the HA. It decreases the synthesis of prostaglandin and bradykinin, and acts directly and indirectly on the effects of substance P and calcium channels. It then generates a short circuit between the nerve endings of mast cells and neutrophils.

So, we know that Viscosupplementation increases the endogenous HA synthesis of proteoglycans and that it is highly important that we know this. It provides hydric protection, and it reduces the expression of prostaglandins, interleukin 1, tumor necrotizing factor, it increases the anti-oxidant effects, it protects against the effects of free radicals.

We already know that in inflammatory components, as we increase the concentration and molecular weight of hyaluronic acid, the better the result for pain, and the better the inhibition of the arachinoic acid cascade, improving inflammation, and protecting cartilage.

On the cellular effects of viscosupplementation, it reduces lymphocyte and leukocyte motility and motility, it reduces the phagocytosis capacity of the macrophage, it reduces the degranulation capacity of the neutrophil, and increases the defense and aggregation of the neutrophils, thus suppresses chondral degeneration, and promotes synovial and meniscal regeneration.

Viscosupplementation with hyaluronic acid has been used since 1980 to preserve joint health, and each year that passes shows that we are on the right track to prevent arthrosis from affecting more and more individuals in their productive phases.