

MRI in Degenerative Joint Disease (DJD): A Proposal for Imaging Standardization in Regenerative Medicine

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Background

In the last few years, clinical applications of regenerative medicine have been increasing their way in medical practice.

Concerning treatment of Osteoarthritis (OA), regenerative medicine is going to change the clinical approach and the possible therapeutic options especially in Degenerative Joint Disease (DJD).

The understanding of extracellular matrix mediators as GFs, nucleotides and Hsps able to stimulate local MSCs, have been going hand in hand with tissue engineering and scaffolding. These recent knowledge in tissue regeneration and self-repairing processes are more and more making their way from the experimental research to the clinical practice.

In our original research and clinical application we have made up a biomaterial composed by Polydeoxyribonucleotides (Pdrn), Hsps and a thickening-scaffolding substance finally being called Gel -Repairer. It works as a local Mesenchymal Stem Cells (MSCs) activator, ultimately generating connective tissue renewal [1,2].

Extracellular Microenvironment

Gel-Repairer plays its role in the extracellular microenvironment.

This space is usually deemed to be outside the plasma membranes, and occupied by fluid and matrix.

Specifically the Extracellular Matrix (ECM) is a substance produced by cells in the extracellular space. It is a main component of the human body. Collagen fiber - a basic component of extracellular matrix material - represents 25 to 30% of the total protein mass of our body. It serves to reinforce the body structure and plasma membranes so that we can withstand gravity and tension, and plays a key role for being an adhesive substance and a signaling molecule for cells aggregation and communications. This material has many constituents such as told Fibrous Components, Glycosaminoglycans, Proteoglycans and Glycoproteins [3,4].

In addition in the extracellular space have been found different metabolites and byproducts, ions, various proteins and non-protein substances (i.e. fragments of DNA, RNA, lipids, microbial products etc.) that strongly affect cellular functions, their survival, apoptosis and cell's replacement [5].

Gel Repairer

Gel Repairer exerts its action in the extracellular microenvironment, working through a prolonged action of proliferative and differentiate stimulus on resident MSCs. It's making substances Polydeoxyribonucleotides, Hsps and local - trauma induced- Growth factors together with the scaffolding function of the Gel on the activated stem cells, finally produces a structural change of the joint's tissue.

The Gel is positioned over the ligament bursa tissue with the aim of activating clusters of residential MSCs located in different spots into the joint tissue.

The activation and differentiation of MSCs is evident by now in literature and in our experience, and consistent data have been reported *in vitro* and in experimental studies. Lines of fibroblasts, osteoblasts and chondroblasts have been found in various conditions of joint MSCs stimulation. The

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process of cell differentiation leads to generate new-making proteins such as collagen (I-II type), elastin and healthy ECM production [2].

Tissue modifications result in increased flexibility of the joint capsule and ligaments. An improvement of the compliance of the bursa leads to a reduction in the intra-articular pressure and, consequently, of pain. Another effect of the Gel probably occurs on the sub-periosteal cluster of MSCs, inducing proliferation and cartilage-bone repair [1].

Assessment and Standardization of Results

The objective measurements of the clinical results are still a main problem in this field and standardization would be vital to come out from empiricism to addressing evidences of clinical results.

Questioners may be considered appropriate to assess the clinical outcomes in terms of pain, stiffness, mobility and grade of disability.

However imaging findings might be vital to demonstrate, standardize and following up the improvement or failure of the joint tissue that we aimed to recover. Specifically we can say that our preferred markers of tissue restoration are modifications in capsule-bursa tissue, the cartilage layer, the bone distortions and bone marrows rearrangements.

It seems quite odd that X-rays are still nowadays almost solely accepted and standardized as criterion to confront orthopedics outcomes. That would be reasonable considering trauma, prosthetic surgery, osteomyelitis, and congenital or vascular bone’s problems.

We deem that X-rays are utterly inadequate to study, measure and compare clinical results in regenerative medicine.

In OA patients are classified following the Kellgren and Lawrence Scale (K&L) for radiological X-rays assessment of DJD. The scale defines four pathological degrees for OA: Grade I: doubtful narrowing of joint space and possible osteophyticclipping. Grade II: definite osteophytes, definite narrowing of joint space. Grade III: moderate

multiple osteophytes, definite narrowing of joint space, some sclerosis, and possible deformity of bone contour (pre-ankylosis). Grade IV: large osteophytes, marked narrowing of joint space, severe sclerosis and deformity of bone contour (ankylosis) [6,7].

These assessment criteria just show a minimal part of the story. Indeed it is impossible to catch all the minimal joints modifications that have great biological and clinical meaning through traditional radiological analysis, given that most of the impact occurs on soft tissue as the fibro-cartilaginous compartment and the capsula-ligament tissue.

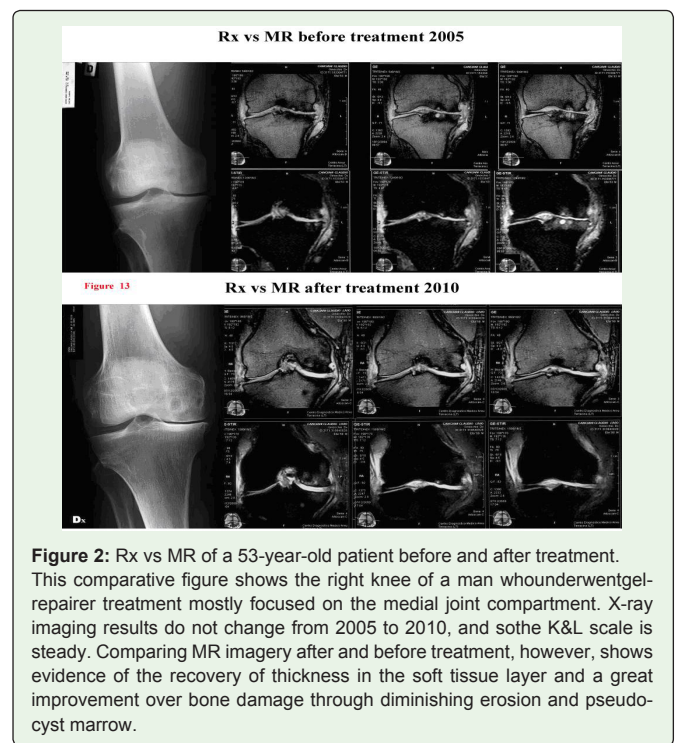
X-rays give precise information only in case of degenerative chondrocalcinosis. In this case the radiological opacities of the calcium deposits in the cartilage layer seem to be related with grade of OA degeneration. Sometimes, after regenerative treatment X-rays shows the reabsorption of calcium deposits which is an indirect sign of tissue activation and possible regeneration (Figure 1).

Patients that seem to reverse and improving their K&L grade after regenerative procedure, there are considered of undetermined significance and not reliable as a marker of real tissue upgrading.

MRI Scan as Imaging Golden Standard

MRI should be the standardized imaging able to catch joint soft tissue modifications. In fact MRI shows the fibro-cartilaginous layer and in case of regeneration, the formation of the “neo cartilaginous matrix”. The intensity of the signal of the neo-matrix is similar in MRI, to that produced by the original. Furthermore the color in the grey scale from white to black is an additional indicator to define the quality of regenerating tissue in comparison to the natural cartilage.

The thickness of the bursa-capsule is a very important parameter; it generally increases its thickness with chronic inflammation. The



measure of this joint component before and after treatment is a significant indicator of the reversal of the disease.

Traditional radiology has major limits in its ability to highlight the structural modifications of soft tissue that become apparent when X-ray and MR images of the same patient are compared. We believe that the greater specificity and sensitivity of MRI will increase the percentage of patients showing a real down staging of DJD, once standard criteria will be introduced (Figure 2).

Basic MRI parameters to be introduced in Regenerative Joint Surgery:

- 1) Thickness of capsule and bursa tissue
- 2) Thickness of cartilage layer measured in three coronal plans (anterior, midline and posterior)
- 3) Color Grey scale (from white to black) of the cartilage layer
- 4) Bone erosion and pseudo-cyst marrow monitoring

In conclusion our proposal is to introduce MRI as golden standard and objective criterion for the measurement of structural joint modifications, which may happen in mid or long term after regenerative tissue procedures.

The above listed four basic factors may be a first and easy proposal, which after the introductions of appropriate units of measures would allow to quantitatively determining the effectiveness of tissue regenerations in the treated joints.

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