

# Biological Surgery as a Treatment for Knee Osteoarthritis

**Mustafa Yassin<sup>1</sup>, Avraham Garti<sup>1</sup> and Dror Robinson<sup>1\*</sup>**

<sup>1</sup>Department of Orthopedics, Rabin Medical Center, Israel

**\*Corresponding author:** Dror Robinson, Department of Orthopedics, Rabin Medical Center, Israel. Email: dror61@gmail.com

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Osteoarthritis (**OA**) is a degenerative disease in which the articular cartilage is affected among other organs. The disease actually involves the subchondral bone to such an extent, that some authors have theorized the principal tissue affected is the bone [1-6]. In fact the changes in the joint involve all tissues including the nerve control of the joint motion, which is particularly important in the unstable joint: “ipsilateral sensation is not important in protecting the stable joint from OA but is necessary to protect the unstable joint from rapid deterioration” [7]. Another structure that is affected in osteoarthritis of the knee is the meniscus that frequently undergoes an extrusion process. The damage to the meniscus, exposes the articular cartilage to excessive forces and leads to degeneration of the articular surface as well as increased joint instability [8-10].

# POTENTIAL REVERSIBILITY OF THE ARTHRITIC PROCESS

Some evidence exists that the osteoarthritic process is partially reversible. Improving gait and normalization of innervation abnormalities might ameliorate symptoms and possibly even reverse structural damage [11-13]. Implantation of a meniscal allograft seems to offer the possibility to regenerate some of the destroyed cartilage [14]. Other treatment options in osteoarthritis, involves the restoration of the affected subchondral bone. The mechanical overload that initiates microdamage of the subchondral bone provokes a biological response that potentiates the progression of articular cartilage damage in OA. Microcracks will cause the initiation of targeted remodeling, accounting for the increased turnover and reduced material density of the subchondral plate. The resultant thinning of the articular cartilage exposes the bone to higher forces and leads to increased bone damage and a vicious cycle ensues [3]. A major player, in this vicious cycle appears to be the Mesenchymal Stem Cells (**MSC**). These cells residing in multiple joint structure including the cartilage, Hoffa's fat pad and subchondral bone, appear altered in osteoarthritis [15]. Their gene expression pattern is altered and this appears to perpetuate joint structure deleterious changes.

## BIOLOGICAL SURGICAL ALTERNATIVES

Autologous Dual-Tissue Transplantation (**ADTT**) is a surgical method for the treatment of osteochondral defects in osteoarthritis involving the use of two types of tissues with at least two types of live stem cells (chondroprogenitors and osteoprogenitors) [16]. The presence of cartilage chips in an osteochondral defect facilitated the formation of fibrocartilage as opposed to fibrous tissue. However the lack of ability to regenerate articular cartilage casts serious doubts about the long term prognosis of this repair tissue.

Osteoarthritic bone tissue contains increased denatured collagen and has reduced matrix mechanical properties, leading to subchondral stiffening that is compatible with the process of normal bone adaptation to mechanical stresses [4]. To improve the mechanical properties of the subchondral bone, subchondroplasty, involving injection of bone substitute into the areas of bone marrow lesions observed during magnetic resonance imaging [17], has been advocated. The mechanism of action appears to be bolstering of the bone [15] mechanism appears to be more effective than anti-inflammatory treatment in preventing cartilage loss in an animal model [18].

## STEM CELL USE IN OSTEOARTHRITIS

As the pathological mechanism in osteoarthritis appears to involve multiple tissues, it appears that the best method of biologically reconstructing the joint should involve instillation of stem cells. The stem cells might be either fat pad derived or bone marrow derived. Some evidence exists that mesenchymal stem cells are abnormal in osteoarthritis and in Bone Marrow Lesions (**BML**). Aberrant Multipotential Stromal Cell (**MSC**) responses within bone tissue contribute to BML pathophysiology. BML appear to be associated with cartilage surface damage and greater

trabecular bone area [15]. The cells themselves when cultured *in vitro* appear to exhibit decreased mineralization capacity. Furthermore, MSC in BML are CD271+ [19]. This cell type accumulation occurs in bone adjacent to cartilage defects and areas of osteochondral angiogenesis [15]. The importance of this CD271+ cells is due to the proinflammatory properties of these cells [20]. It appears that the presence of increased numbers of perivascular MSC in osteoarthritis might be responsible for the low grade inflammation of the synovial tissue. A possible connection to pain is suggested by the nature of the CD271 molecule. CD271 (also named as low-affinity nerve growth factor receptor) is a receptor for neurotrophins, which stimulate neuronal cells to survive and differentiate. Increase nerve endings are a typical for osteoarthritic joints.

When considering the use of MSC's in the treatment of osteoarthritis, the cells should not be culture expanded. It appears that culture expansion is associated with phenotypic and functional "drifts" that occur in MSC preparations as they are taken out of their native bone marrow microenvironment and induced to proliferate *in vitro* [21].

## DISEASE MODIFICATION USING MSC

During the last few years use of MSC has been advocated for the treatment of early osteoarthritis. Adipose derived stem cells appear to allow restoration of articular surface in rabbit experimental osteochondral defect model [22]. An alternative approach was suggested by Sanchez et al. [23] involving the injection of Platelet Rich Plasma (**PRP**) into joints and the subchondral bone. The rationale appears to be the induction of a multifactorial healing reaction involving different tissue crosstalk.

The use of bone marrow derived MSC's appears to make sense if the bone marrow in the vicinity of the osteoarthritic process appears to be abnormal. Such use must be accompanied by behavior modification, foot wear changes [11] and alteration of the metabolic environment from glucose utilization into fatty acid utilization with restoration of mitochondrial function [24,25] preventing chondrocyte apoptosis. Chondrocyte apoptosis appears to take place in osteoarthritis [26]. It is not clear whether chondrocyte apoptosis is the inducer of cartilage degeneration or a byproduct of cartilage destruction. Chondrocyte death and matrix loss may form a vicious cycle, with the progression of one aggravating the other, and the literature reveals that there is a definite correlation between the degree of cartilage damage and chondrocyte apoptosis. Restoration of mitochondrial function might allow normalization of autophagy, a mechanisms that seems to be inhibited in osteoarthritis [27].

## AUTHORS' EXPERIENCE USING BONE MARROW DERIVED MSC'S

The authors are currently using the BioCue system (Biomet) for bone marrow MSC's isolation [28]. To date 12 patients with Kelgren Lawrence grade 3 osteoarthritis were treated (8 males, average age 54±9 years). The treatment involves knee arthroscopy to treat any mechanical cause of symptoms and joint surface debridement. Simultaneously bone marrow is aspirated

from either the proximal femur or the iliac crest. At least 60 milliliters are aspirated and MSC are isolated using the BioCue device. The MSC are injected into the chondral surface defects as well as into the subchondral tibia surface.

## SUGGESTED REHABILITATION PROTOCOL

Post-operative ice packs and continuous passive motion is performed for the first 48 hours. The patients are instructed to toe-touch for the first four weeks. Exercises are an essential part of the post-operative protocol. Early on Transcutaneous Electrical Muscles Therapy (**TENS**) is instituted. From the third day post op, isometric strengthening is performed. From the fifth post-operative week closed chain exercises are performed. The minimal exercise time recommended is two hours per day, though this appears to be a difficult hurdle.

The patients are instructed to follow a low-carb diet, and supplements are recommended including vitamin B complex, carnitine, magnesium, selenium and boron.

## PATIENT OUTCOME FOLLOWING BONE MARROW MSC'S IMPLANTATION

Overall KOOS score improved from 33±21 at baseline to 63±16 at six months and 74±12 at one year. VAS score improved from 8±3 at baseline to 5±3 at six months and 3±3 at one year postoperative.

Joint space (measured on a standing long leg x-ray) was maintained at one year postoperative.

## CONCLUSIONS

Biological modification of osteoarthritis disease progression appears to require treatment of not only the obvious cartilage defects but the abnormal subchondral bone and the decreased oxygen utilization due to mitochondrial dysfunction. The instillation of bone marrow stem cells appears to improve patient joint function and should be combined with dietary modification to shift the overall metabolism toward aerobic metabolism supporting autophagy of abnormal cartilage and tissue reconstitution.

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