

# Biological surgery as a treatment for knee osteoarthritis short term results of bone marrow derived stem cell implantation

## Abstract

Mesenchymal stem cells appear to be involved in the osteoarthritic process. Some evidence suggests that the stem cells are altered in osteoarthritic joints. The current study aimed to investigate whether application of mesenchymal stem cells derived from bone marrow, might ameliorate function and pain following joint arthroscopy and resolution of any mechanical issues.

A single-center cohort of patients was analyzed. The inclusion criteria were symptomatic knee osteoarthritis in a patient aged 65 or younger; KOOS pain score of 60 or less following a failure of a three-month conservative therapy regime, and consent by the patient to undergo knee arthroscopy. Patients included in this cohort were treated according to a uniform protocol. Under general or regional anesthesia, a knee arthroscopy was performed. Any mechanical causes of symptoms were treated (degenerative meniscal tears, cartilage flaps, osteophytes or loose bodies). Following the arthroscopy, 60 ml bone marrow were aspirated from the distal femur or proximal tibia, concentrated using the Biomet Bio Cue system (Warsaw, Indiana) and 5-7ml were injected into the knee joint via the sutured arthroscopic portal. Post-operatively weight bearing was restricted for four weeks and intense physiotherapy regimen focused on mobility and muscle strengthening was initiated. Patients were assessed by the KOOS questionnaire and the Objective IKDC physical examination questionnaire. Responder analysis was performed with treatment response defined as increase over baseline of more than 10 overall KOOS points at the last follow-up time point.

12 patients (average 54±6.6) underwent this procedure and were assessed pre-operatively, and following 3 months and 6 months using the KOOS patient reported questionnaire as well as the IKDC surgeon objective outcome score. The patients tolerated the procedure well, and no adverse events were noted. The KOOS pain subscale improved from 42.7±5 to 51.6±5.6 at 3 months and 62.6±8.3 at 6 months. The overall KOOS scale as a measure of a combined pain and function measure improved from 42±4.6 to 51.5±5.2 at 3 months and 62.6±8 at 6 months. Overall responder rate was 41% at 3 months and 91% at 6 months.

In conclusion in a small cohort of patients, bone marrow aspirate concentrate appears to improve short term pain and function in osteoarthritic patients, and might postpone joint replacement.

**Keywords:** Osteoarthritis, Meniscal, Mesenchymal, Arthroscopy, Questionnaire, Subchondral, Microcracks, Osteoarthritis

**Abbreviations:** MSC, Mesenchymal Stem Cells, BML, Bone Marrow Lesions, TENS, Electrical Muscles Therapy, OA, Osteoarthritis

## Introduction

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.<sup>1-6</sup>

While for many years it was assumed that the osteoarthritis process is unidirectional, some current evidence points to the potential reversibility of the process. Improving gait and normalization of innervation abnormalities might ameliorate symptoms and possibly even reverse structural damage.<sup>7-9</sup> 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.<sup>3</sup> 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.<sup>3</sup> A major factor, in this vicious cycle appears to be mesenchymal stem cells (MSC) activation. These cells residing in multiple joint structure including the cartilage, Hoffa's fat pad and subchondral bone, appear altered in osteoarthritis.<sup>10</sup> Their gene expression pattern is altered and this appears to perpetuate joint structure deleterious changes.

## 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.

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Some evidence exists that mesenchymal stem cells are abnormal in osteoarthritis and in bone marrow lesions (BML). BML appear to be associated with cartilage surface damage and greater trabecular bone area.<sup>10</sup> The cells themselves when cultured in vitro appear to exhibit decreased mineralization capacity. Furthermore, MSC in BML are CD271<sup>+</sup><sup>11</sup> This cell type accumulation occurs in bone adjacent to cartilage defects and areas of osteochondral angiogenesis.<sup>10</sup> The importance of this CD271<sup>+</sup> cells is due to the pro inflammatory properties of these cells.<sup>12</sup> 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.

## Methods

This study concerns a consecutive cohort of patients treated using the BioCue system (Biomet) for bone marrow MSC's isolation.<sup>13</sup> To date 12 patients with Kelgren Lawrence grade 3 osteoarthritis were treated (9 males, average age 54.2±6.6 years) (Table 1). 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 joint space.

## 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 due to its possible anti-inflammatory effect, and supplements are recommended including vitamin B complex, carnitine, magnesium, selenium and boron. The purpose of the supplements is to both allow muscle mass build-up as well as improve joint health due to the addition of micro-minerals needed for joint homeostasis.

## Outcome evaluation

Patients were assessed pre-operatively and after 3 months and 6 months using the KOOS questionnaire as well as the IKDC Knee Examination Form. The overall KOOS Minimal Important Change (MIC) is currently suggested to be 8-10 (KOOS User's Guide 1.1 Updated August 2012). Change has been defined as a 10 points change. In addition a high clinical response was defined as more than two standard deviations, i.e. more than 20 points improvement in KOOS at last available follow-up time point.

## Statistical evaluation

The Analyse-it statistical add-on of Microsoft Excel was used (<http://analyse-it.com/>). Descriptive statistics are reported as mean±standard deviation. Significance level was defined at the 0.05 level. Continuous variables were analyzed by ANOVA and non-parametric ones by Kruskal-Wallis test.

## Results

### Patient outcome following bone marrow MSC's implantation

Overall KOOS score significantly improved from 42.7±5 at baseline to 51.6±5.6 at three months and 62.6±8.3 at six months (p<0.0001). Post hoc analysis (Tukey) indicated that the significance improvement occurred both from 0 to 3 months as well as from 3 to 6 months. This appears to indicate that the improve trend continues at least up to 6 months after treatment. Other KOOS subscales are reported on (Table 2). The IKDC grade was almost uniformly grade D pre-operatively and significantly improved at 6 months follow-up. The number of patients with effusion declined as well from 12/12 patients at baseline to 6/12 patients at 6 months post-op.

**Table 1** Patient Demographics

Demographics (n=12)	
Gender	9 Males
Age	54±6.6 Years
Baseline KOOS Overall Score	42.7±5.7
Baseline KOOS Pain Subscale Score	51.5±13.7
Baseline Knee Examination Grade	Grade C n=3, Grade D n=9
Effusion	Minimal n=8, Moderate n=3, Severe n=1

**Table 2** KOOS overall Score and Subscales and IKDC Grade per Time-point

KOOS Score	Baseline	3 Months Post Operation	6 Months Post Operation	Significance I-way ANOVA
KOOS Overall	42.7±5.2	51.6±5.6*	62.6±8.4*	I-way ANOVA p<0.0001
KOOS pain Subscale	51.5±3.5	75.7±3.8*	77.9±3.7*	I-way ANOVA p<0.0001
KOOS Symptoms Subscale	52.4±14.9	56.6±16.1	65.9±18.2	I-way ANOVA n.s.
KOOS ADL Subscale	60.3±16.4	65.2±17.7	76.7±11.3*	I-way ANOVA p<0.039
KOOS QOL Subscale	25.2±14.2	34.7±11.7	56.7±16.3*	I-way ANOVA p<0.001
KOOS Sports & Recsubscale	23.3±9.9	25.1±10.7	36.1±11.7*	I-way ANOVA p<0.0135
IKDC Knee Examination	Gr. C=3 Gr. D=9	Not relevant due to rehabilitation protocol	Gr. B=4 Gr. C= 6 Gr. D=2*	Kruskal-Wallis X2 statistic 19.37, p<0.001

## Discussion

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.<sup>14</sup> Oxidative stress-mediated post-translational modifications of redox-sensitive proteins are postulated as a key mechanism underlying age-related cellular dysfunction and disease progression. Results of the current study (though limited in number of treated patients and short follow-up period) indicate that injection of bone marrow cells improves patients function and ameliorates pain. The improvement is apparently related to decrease in knee effusion. The instillation of bone marrow stem cells should be combined with dietary modification to shift the overall toward aerobic metabolism supporting autophagy of abnormal cartilage and tissue reconstitution. The metabolic shift might allow better tissue regeneration. A study in rats apparently demonstrates that SIRT-3

upregulation seems to protect against osteoarthritis.<sup>15</sup> Specifically, SIRT3 mediates age-related changes in cartilage redox regulation and protects against early-stage OA. Up regulation of SIRT-3 can be induced by dietary modification and certain supplements. The current study appears to indicate that bone marrow instillation in moderately osteoarthritic knees combined with appropriate exercise regimen and dietary supplements might allow improved function. Further randomized studies should be performed in order to assess whether it is possible to prevent the need for knee arthroplasty in such patients.

## Acknowledgments

None.

## Conflicts of interest

None.

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