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Longitudinal evaluation of synovial fluid and synovial fluid MSC transcript changes in subjects undergoing joint distraction

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Background. In relatively young patients with end-stage knee osteoarthritis (OA), total knee arthroplasty (TKA) comes with the risk of future revision surgery [1]. Knee joint distraction (KJD) is a joint preserving surgical technique, which has been shown to provide clinical and structural improvement for over five years [2,3] and postpones the need for TKA. The underlying mechanism however, is largely unknown. It is anticipated that an alteration of joint homeostasis including synovial fluid resident mesenchymal stem cells (MSCs), and their access to the superficial arthritic surface, is key to the regenerative process seen with KJD.

Objectives. To evaluate the longitudinal changes in synovial fluid MSC numbers and their gene expression profile upon KJD.

Methods. Patients with established symptomatic radiographic knee OA undergoing KJD gave written informed consent to participate. Synovial fluid (SF) was sampled at baseline (before distraction; pre), at midpoint (after 3 weeks; during) and at endpoint of distraction (6 weeks; post). MSCs were isolated and Colony Forming Units (CFU; MSCs) were determined. Moreover, gene expression profiles in isolated synovial fluid (SF) MSCs was determined by Realtime PCR for genes known to be involved in joint morphogenesis, cartilage homeostasis and OA, which included: Aggrecan (ACAN), Growth/Differentiation Factor 5 (GDF5), Gremlin 1 (Grem1), Parathyroid Hormone 1 receptor (PTH1R), Discoidin Domain receptor 2 (DDR2), A disintegrin and metalloproteinase with thrombospondin motifs 4, Aggrecanase 1 (ADAMTS4), SRY-related proteins 9 (SOX9), Fatty acid binding protein 4 (FAB4), and Parathyroid hormone-related protein (PTHrP). All data were normalized to HPRT ($2^{-\Delta Ct}$).

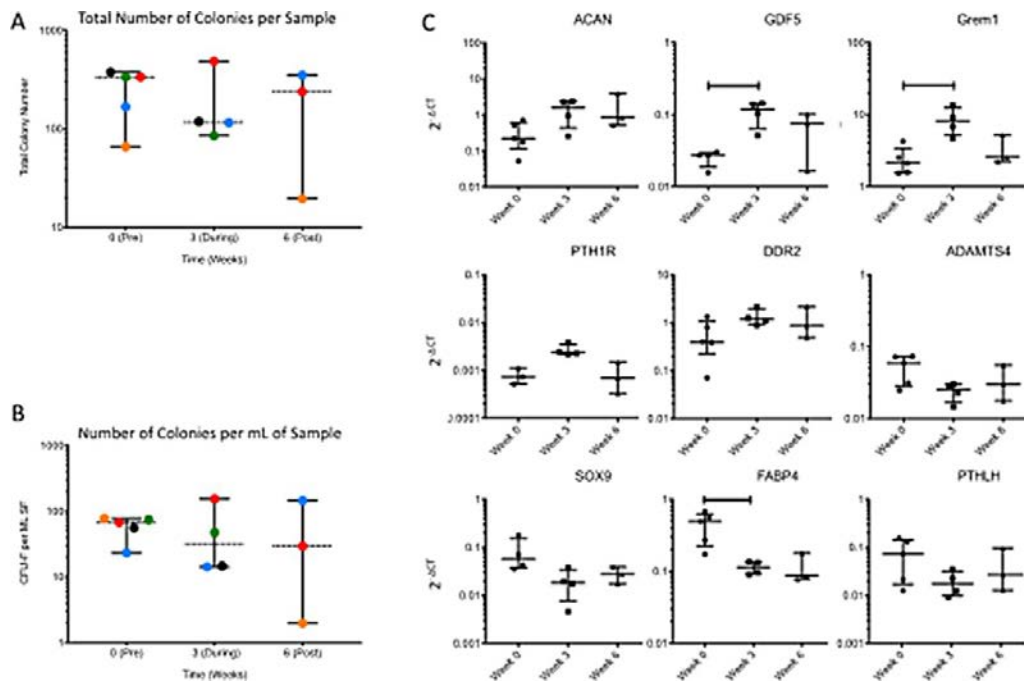


Figure 1

Changes in synovial fluid MSCs numbers and gene expressing profiles upon knee joint distraction. Bar indicates statistically significant changes ($p < 0.05$)

Results. Participants had a mean age 47 ± 9 yrs and 6 out of 7 (86%) were female. All had KL grade ≥ 2 with substantial knee pain at baseline. Enough SF ($> 500 \mu\text{l}$) could be obtained from $n=7$ at baseline, $n=4$ at midpoint, and $n=3$ at endpoint of distraction. For the first time in this same group, we show how MSC number initially decline upon KJD (figure 1A-B) as seen previously in our animal study [4]. Also, MSCs present in the SF showed changes in their gene expression profile upon KJD, most clearly observed during the treatment (3 weeks; figure 1C). GDF5 and Grem1 presented with a statistically significant increased expression ($p < 0.05$) during treatment while FAB4 expression was decreased. ACAN, PTH1R, and DDR expression had the tendency to increase over time. ADAMTS4, SOX9 and PTHLH expression showed a trend to decrease over time..

Conclusión. This explorative study provides for the first-time data on changes in SF MSC number and their gene expression profiles upon knee joint distraction. As such, first clues are provided for the involvement of MSCs in the regenerative process induced by joint distraction for end-stage knee OA. The fall in SF MSCs number during distraction suggests adhesion to the arthritic surfaces in the KJD environment as found in our previous work in canine KJD [4]. Further studies are necessary to unravel the processes involved.

References. [1] SM Kurtz, et al. Clin Orthop Relat Res 2009, 467 (10): 2606-
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