**Assessment of candidate predictive protein biomarkers for microfracture and osteotomy**

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**Purpose (the aim of the study)**

Biomarkers that can predict clinical outcome for surgeries to prevent the progression of osteoarthritis (OA) are needed to ensure patients can be better stratified to receive the most appropriate treatment. We have previously identified biomarkers that have the potential to predict patient outcome to autologous chondrocyte implantation (ACI), a cell-based therapy for cartilage defects in the knee, when combined with known demographic risk factors of success/failure. However, ACI can only be offered at specialist hospitals; therefore this study aims to investigate the potential of a panel of protein biomarkers for the prediction of clinical outcome following treatment using the more routine and accessible surgeries, microfracture and osteotomy.

**Methods**

Concentrations of biomarkers known to relate to OA severity or with predictive value in ACI treatment (cartilage oligomeric matrix protein (COMP), hyaluronic acid (HA), soluble CD14 (sCD14), aggrecanase-1, S100 calcium binding protein A13 (S100A13) and matrix metalloproteinase (MMP)-1 and 3) were assessed in the synovial fluid (SF) of 22 and 21 patients prior to microfracture or osteotomy, respectively, using commercial immunoassays (an activity assay was used to assess aggrecanase-1). SF total protein concentration was also assessed using Pierce 660nm reagent (Thermo Fisher). Levels of COMP and HA were also measured in the plasma of these patients. Biomarker concentrations have been correlated with baseline and 12 month post-operative Lysholm scores, where available (osteotomy, n=18; microfracture, n=13) in a preliminary assessment of their predictive value.

**Results**

In patients treated with either surgery, baseline plasma COMP concentrations correlated with baseline Lysholm score (*p*=0.030; r=-0.39; Pearson correlation). In patients treated with microfracture, baseline aggrecanase-1 (p=0.03; r=0.501; Pearson correlation) and total protein (p=0.03; r=0.526; Pearson correlation) concentrations in SF correlated with baseline Lysholm score. S100A13 concentration in pre-operative SF correlated with 12 month post-osteotomy Lysholm scores (*p*=0.019; r= -0.662; Pearson correlation), as did baseline total protein concentration (*p*=0.028; r=-0.638; Pearson correlation).

**Conclusions**

Plasma COMP concentration is known to be elevated in OA and when assessed in this study inversely correlated with baseline Lysholm score when surgery groups were combined. Somewhat surprisingly, aggrecanase-1 and total protein concentrations (also OA indicators) correlated directly with baseline Lysholm score in microfracture treated patients. Perhaps most interestingly, our preliminary assessments indicate that baseline S100A13 and total protein may be informative of post-operative Lysholm score in osteotomy patients. Together these findings warrant further investigation and validation in larger patient cohorts.