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FRI0405

CARTILAGE BIOMARKERS S-COLL2-1 AND S-COLL2-1NO2 ARE HELPFUL IN IDENTIFYING KNEE OSTEOARTHRITIS PATIENTS AT RISK OF DISEASE WORSENING

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Background: Coll2-1 is a peptide of 9 amino acid located in the triple helix of type II collagen molecule reflecting cartilage degradation (1). Coll2-1NO2 is the nitrated form of Coll2-1 and considered as a biomarker of the inflammatory-related cartilage degradation (2). This peptide is involved in osteoarthritis physiopathology since it was demonstrated that Coll2-1 induced synovitis in rat.

Objectives: To identify if biochemical markers s-Coll2-1 and s-Coll2-1NO2 are associated to knee osteoarthritis (OA), focusing on pain, function as well as structural features assessed by MRI in various knee compartments and to assess their ability at predicting knee OA worsening.

Methods: 116 subjects with knee OA were followed during one year with pain, function and MRI evaluation (PRODIGE study, NCT02070224). Type II collagen-specific biomarker Coll2-1 and its nitrated form Coll2-1NO2 were directly measured in serum using immunoassays at baseline and after three, six and twelve months follow-up.

Results: sColl2-1 and sColl2-1NO2 were associated to several baseline knee features quantified with Whole-Organ Magnetic Resonance Imaging Score (WORMS). S-Coll2-1 was significantly correlated with bursitis ($r=0.29$, $P<0.01$), bone attrition ($r=0.25$, $P=0.01$), cysts ($r=0.24$, $P=0.02$) and cartilage ($r=0.23$, $P=0.03$) WORMS sub-scores for the whole joint as well as with the medial femorotibial joint sum score ($r=0.26$, $P=0.01$) and medial femorotibial joint cartilage ($r=0.23$, $P=0.02$). s-Coll2-1NO2 was correlated with WORMS total score ($r=0.23$, $P=0.02$), WORMS scores in the patellofemoral ($r=0.23$, $P=0.02$) and medial femorotibial compartments ($r=0.21$, $P=0.03$) and with osteophytes scores ($r=0.27$, $P<0.01$). Baseline s-Coll2-1NO2 was higher in subjects with a pain worsening (426.4 pg/mL [278.04-566.95]) as compared to non-progressors (306.84 [200.37-427.84]) over one year (AUC=0.655, $P=0.015$).

Conclusion: Cartilage biomarkers s-Coll2-1 and s-Coll2-1NO2 are associated to several knee OA features quantified with WORMS scoring system on MRI. Serum values of Coll2-1NO2 are also associated to a worsening of target knee pain over one year. Coll2-1 and Coll2-1NO2, in association with other structural features, pain and function, could help at identifying OA phenotypes and patients at risk of OA worsening.

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FRI0406

CARTILAGE REPAIR ACTIVITY DURING JOINT-PRESERVING TREATMENT MAY BE ACCOMPANIED BY OSTEOPHYTE FORMATION

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Background: Knee joint distraction (KJD) is a joint-preserving treatment to postpone total knee arthroplasty (TKA) and has shown cartilage repair and clinical improvement in patients with severe knee osteoarthritis (OA), as has high tibial osteotomy (HTO). The observed cartilage repair activity could be related to an increase in transforming growth factor- β 1 (TGF β -1), which increases in the synovial fluid (SF) during KJD treatment.¹ However, animal and ex vivo human studies have shown that TGF β -1 also induce formation of osteophytes, generally seen as an OA severity hallmark. Similarly, interleukin-6 (IL-6) was observed to increase in SF during KJD treatment and may also be associated with osteophytosis.

As such, we hypothesized that joint-preserving regenerative treatments demonstrating cartilage repair activity lead to general tissue (re)generation, including osteophytosis.

Objectives: To analyze osteophytosis after KJD and compare this to HTO and natural progression in knee OA.

Methods: 63 KJD patients were included in several clinical trials, one of which was a randomized controlled trial comparing patients indicated for HTO, but treated with KJD (KJD_{HTO}; n=23) vs. patients treated with HTO (n=46). All patients received standardized radiographs before and one and two years after treatment, used to measure osteophyte size. Only patients with measurements at baseline and two-year follow-up were included. As a control group for natural progression, untreated knee OA patients from Cohort Hip & Cohort Knee (CHECK; n=1002) were studied. Only patients who received a TKA during follow-up were included, using their last two measurements before treatment to reflect natural two-year progression (n=44).

A separate group of 20 patients treated with KJD in regular care underwent SF aspirations before and after treatment, and TGF β -1 and IL-6 levels were measured by immunoassay (Mesoscale Discovery). Unstandardized radiographs were acquired before and one year after treatment, used to score osteophytes with the revised Altman score, resulting in a 0 (normal) to 12 (severe) whole-joint score. Only patients with radiographs and SF aspirations at both baseline and one-year follow-up were included.

Results: After two years, both KJD (n=58) and HTO (n=38) patients showed a significant increase in osteophyte size (+6.2mm² and +7.0mm² resp.; both $p<0.003$; figure 1), with no significant differences between the treatments ($p>0.38$). Untreated CHECK patients who underwent TKA did not show significant two-year osteophyte changes before treatment (+2.1mm²; $p=0.207$; figure 1) and showed significant differences compared with KJD and HTO groups (both $p<0.044$). In the KJD SF aspiration group (n=17), the Altman osteophyte score was not different at one year compared to baseline (+0.2 points; $p=0.653$) and there was no association between baseline biomarker values and the baseline Altman osteophyte score, or between changes in these parameters (all $p\geq 0.28$). Trichotomization of patients in groups with a decrease, no change or increase in total Altman osteophyte score indicated that there was a statistically significant difference between the three groups in changes in TGF β -1 ($p=0.044$; figure 2A), but not IL-6 ($p=0.898$; figure 2B).

Conclusion: After KJD treatment, joint space widening and clinical improvement are accompanied by osteophytosis. Similar results were observed after treatment with HTO, suggesting effects occur in regenerative joint-preserving

treatments in general. The increased osteophytosis may be a bystander effect of cartilage repair activity related to intra-articular factors like TGF β -1 and questions whether osteophytosis should necessarily be considered a hallmark of OA worsening.

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Figure 1: Two year changes in total joint osteophyte size in mm². (A) Osteophyte size after treatment for all patients treated with knee joint distraction (KJD), high tibial osteotomy (HTO), HTO-induced KJD patients (KJD_{HTO}), and for untreated knee osteoarthritis patients before receiving a total knee arthroplasty (CHECK). Mean and standard error of the mean (SEM) are shown, * indicates significant changes ($p < 0.05$) compared to baseline. (B) Two-year osteophyte size changes for individual KJD, HTO, KJD_{HTO} and CHECK patients. Mean and 95% confidence interval are shown, p-values above groups indicate significance of two-year changes.

Figure 2: Box plots for the changes in synovial fluid concentrations during treatment with knee joint distraction, of (A) transforming growth factor- β 1 (TGF- β 1) and (B) interleukin-6 (IL-6), categorized into groups of patients with a decrease, no change or increase in total Altman osteophyte score. The bar represents the median, whiskers represent the minimum and maximum value, the + represents the mean.

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FRI0407

USER-FRIENDLINESS OF A NOVEL DEDICATED KNEE JOINT DISTRACTION DEVICE: EXPERIENCES FROM CLINICAL PRACTICE

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Background: Knee joint distraction (KJD) is a validated surgical technique that aims to postpone arthroplasty for a prolonged time in younger knee osteoarthritis (OA) patients (<65 years). In absence of dedicated devices intended for KJD, this procedure has thus far been performed with general purpose external fixation devices.¹ The demonstrated clinical benefits of KJD raised a clinical demand for a dedicated device (DD), including a desire for increased user-friendliness and decreased treatment burden. As such, in a multi-disciplinary setting with clinicians, patients, and medical device experts, several desired device

characteristics were determined. These included perpendicular positioning of bone pins relative to the longitudinal tibia axis, surgery time < 45 minutes, no protruding parts above the most proximal and below the most distal bone pins, and pin tracts that are accessible for pin tract care. Based on the desired characteristics, a dedicated distraction device was developed and made available for clinical application.

Objectives: To compare user-friendliness between the developed DD and previously used concept device (CD) used in regular care.

Methods: Patients were treated with either the CD (n=22) or DD (n=22) in clinical practice. For both devices, the surgical technique was identical: fixation to the tibia and femur with 8 bone pins (figure 1) and 5mm distraction for 6 weeks. The intervention duration when placing the device (defined as time between first incision and the surgeon being finished) was registered for all patients. After treatment, patients were asked to fill out a custom questionnaire about user-friendliness of the device during treatment, consisting of 25 questions on difficulties performing activities regarding clothing, sleeping, device care, daily activities, movement and complications. Intervention duration was compared between groups using an independent t-test while for questionnaire answers Mann Whitney U tests were used. Chi-square tests were used when comparing (complication) occurrences between groups.

Results: Intervention duration was on average shorter for the DD (44 vs 56 minutes; $p < 0.001$). 34 Patients (16 CD, 18 DD) completed the questionnaire. Patient user-friendliness of the DD was higher rated for 6 questions (all $p < 0.05$), and similar to the CD for the remaining questions (all $p > 0.01$). Besides advantages in daily living activities with the use of the DD, also less pin tract infections were registered with this device (88% of patients with CD vs 56% with DD). Results of all questions are provided in figure 1. Three patients who were treated with both devices (left and right knee, separately and subsequently) generally rated the DD similar to be or slightly better than the CD.

Figure 1: The proof-of-concept (left) and dedicated (right) knee distraction device in use

Figure 2: User-friendliness of the used knee distraction device, the concept device (CD) or dedicated device (DD). For all questions, 10 represents the best (most desired) answer. Statistically significantly different parameters are marked blue. SD: standard deviation; CI: confidence interval.