the probability of superiority to PBO was 80% for CBPI PI and 89% to 96% for secondary endpoints. LYB showed inconsistent separation from PBO across the endpoints, with probability of superiority to PBO 54% to 89%. The separation of carprofen and PBO arms demonstrated assay sensitivity. The incidence of adverse events for LYA (35.9%) was comparable to that of carprofen (25.6%) and PBO (32.6%). For LYB, the incidence was significantly higher versus PBO (59.5%, $P=.017$).

Mean CFB to Week 2 in primary and secondary efficacy endpoints and probability of being superior to PBO				
	LYA (n=39)	LYB (n=42)	Carprofen (n=39)	PBO (n=43)
CBPI PI (Primary)				
LS mean CFB (95% CI)	-1.85 (-2.44, -1.25)	-1.54 (-2.14, -0.95)	-2.12 (-2.73, -1.52)	-1.50 (-2.07, -0.92)
Prob. superior to PBO, %	80	54	93	
CBPI PS				
LS mean CFB (95% CI)	-1.66 (-2.14, -1.18)	-1.39 (-1.87, -0.91)	-1.56 (-2.05, -1.08)	-1.14 (-1.60, -0.68)
Prob. superior to PBO, %	94	78	90	
CBPI OI				
LS mean CFB (95% CI)	0.56 (0.30, 0.82)	0.37 (0.11, 0.63)	0.61 (0.35, 0.87)	0.35 (0.10, 0.59)
Prob. superior to PBO, %	89	56	93	
LOAD Mobility				
LS mean CFB (95% CI)	-6.18 (-8.38, -3.97)	-5.43 (-7.61, -3.24)	-7.52 (-9.75, -5.28)	-3.55 (-5.68, -1.42)
Prob. superior to PBO, %	96	89	99	

CI=confidence interval; LS=Least squares; Prob.=probability

Conclusions: The study results support an efficacy proof-of-concept signal for the mPGEs1 inhibitor mechanism for treatment of chronic OA pain in canine patients.

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SAT0503 CAN BALNEOTHERAPY MODIFY MICRORNA EXPRESSION LEVELS IN OSTEOARTHRITIS? A COMPARATIVE STUDY IN PATIENTS WITH KNEE OSTEOARTHRITIS TREATED WITH MUD-BATH THERAPY

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Background: MicroRNAs (miRNAs) are a class of 19–23 nucleotides long non-coding RNAs that post-transcriptionally regulate the activity of target mRNAs. MicroRNAs are involved in cartilage homeostasis and play an important role in the pathogenesis of osteoarthritis (OA). They have been detected in human plasma and in synovial fluid and are considered as potential diagnostic biomarkers and therapeutic targets of OA. Balneotherapy is a common non-pharmacological treatment for OA patients. In a previous published prospective single-blind randomized clinical trial in patients with knee OA, we showed that a cycle of mud-bath therapy (MBT) in addition to conventional treatments induced an improvement on pain, functional capacity and quality of life in comparison to standard treatment alone.

Objectives: as part of this study we evaluated the whole blood levels of miR-155, 223, 181a, 146a and miR-let-7e, which are involved in the pathogenesis of OA.

Methods: Thirty-two patients aged between 50 and 75 years with knee OA defined by the ACR criteria were included for the current analysis, based on the availability of blood sample at basal time and after 2 weeks. Twenty-one patients (MBT group) were daily treated with a combination of daily local mud-packs at 42°C and baths in mineral water, at 37°C for 15 min, for a total of 12 applications over a period of 2 weeks, in addition to standard therapy; the other eleven patients (control group) continued their conventional treatment alone.

Clinical parameters [global pain score by a 0–100 mm Visual Analog Scale (VAS); physical function, total pain score and total stiffness score (WOMAC)] and microRNAs expression were performed at basal time and after 2 weeks. Peripheral whole blood was collected into PAXgeneTM Blood RNA tubes and then stored at -80°C. Total RNA was extracted using the PAXgeneTM Blood miRNA kit and the relative expression of miR-146a, miR-155, miR-223, miR-181a and miR-let-7e were determined by qRT-PCR.

Results: At the end of MBT we observed a statistically significant improvement of clinical parameters. Furthermore, we observed a significant decrease of miR-155, 181a and miR-146a ($p<0.001$) and of miR-223 ($p<0.01$) expression levels. On the contrary, no clinical and biochemical modifications were detected in the control group. Concerning miR-let-7e expression levels no significant variations were showed in both groups after 2 weeks.

Conclusions: Our data showed that MBT can modify the expression levels of miR-155, 181a, 146a and 223 expression levels, that are up-regulated in OA. This MBT effect could be explained considering the role of the heat stress and of

the hydrostatic pressure, since some miRNAs were found to be temperature and mechano-responsive. Further studies are needed to better explain the mechanism of action of MBT and the role of miRNAs in OA.

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SAT0504 PREDICTIVE ABILITY OF BIOMARKERS LINKED WITH SYNOVITIS FOR FUTURE INCIDENCE OF PAINFUL KNEE OSTEOARTHRITIS IN A COMMUNITY BASED COHORT OF MIDDLE-AGE WOMEN

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Background: Radiographic knee osteoarthritis (RKO) is associated with the knee pain. However, more than half of the middle-aged individuals with RKO will report no concurrent knee pain. Specific matrix metalloproteinases (MMPs) generated protein fragments have been associated with knee synovitis and suggested as specific neo-epitope biomarkers of joint remodelling.

Objectives: The aim of the study was to evaluate the association between MMP-derived neo-epitope biomarkers measured in serum, and future incidence of either painful RKO or RKO without pain, in a cohort of middle-aged women with no RKO at baseline.

Methods: 585 participants (mean age 53.2, mean BMI 25.1) from the Chingford 1000 Women Study Chingford Women Study had serum biomarker levels of MMP- degraded of CRP (CRPM), collagen type II (C2M) and collagen type III (C3M) measured at year 2 or 3 of the study. All participants had a Kellgren Lawrence (KL) score of 0 in both knees at baseline. Ten years following the recruitment, incidence of RKO was determined as KL ≥ 2 and painful RKO was defined as the presence of pain on any number of days in the preceding month in the knee with RKO. Log-transformed normalised biomarker levels were utilised in separate logistic regression models adjusted for age. Outcomes were defined as either RKO without pain or painful RKO. Further analyses were performed adjusting for both age and BMI.

Results: 24.6% of women developed RKO during 10 years after the recruitment, but only 8.9% of developed RKO associated with concurrent knee pain. After adjusting for age, statistically significant positive associations were found between C3M and CRPM and the risk of developing painful RKO with odds ratio (OR) =3.4 (95% confidence interval (CI): 1.4 to 8.2), and OR=2.5 (95% CI: 1.2, 5.2) respectively. After adjusting for age and BMI, only C3M was positively associated with risk of developing painful RKO with OR=3.2 (95% CI: 1.3, 7.8).

Conclusions: In a population of middle-aged women without knee osteoarthritis, an MMP generated neo-epitope of collagen III previously linked with knee synovitis (C3M) can independently identify high-risk individuals for developing painful RKO. These findings indicate that targeting MMP activity may be a promising therapeutic strategy in well-targeted populations.

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SAT0505 SELF-REPORTED KNEE INSTABILITY ASSOCIATED WITH PAIN AND ACTIVITY LIMITATIONS PRIOR AND ONE YEAR AFTER TOTAL KNEE ARTHROPLASTY IN PATIENTS WITH KNEE OSTEOARTHRITIS

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Background: Sixty to 80% of the patients with knee osteoarthritis (OA) reported self-reported knee joint instability, which was associated with pain and activity limitations. One previous randomized control trial described the prevalence of retained self-reported knee joint instability after total knee arthroplasty (TKA) (32%). To better understand self-reported knee joint instability in usual care there is a need to replicate and extend the results.

Objectives: The aims of the study were to determine (i) the prevalence of self-reported knee instability prior and one year after TKA, (ii) the associations between self-reported knee instability, pain, activity limitations and quality of life prior and one year after TKA, (iii) the course of self-reported knee instability over time and (iv) the associations between retained knee instability, pain, activity limitations and quality of life.

Methods: Consecutive patients with knee OA undergoing primary TKA, extracted from the Longitudinal Leiden Orthopaedics and Outcomes of Osteoarthritis Study (LOAS Study), were included. Self-reported knee joint instability and the Knee injury and Osteoarthritis Outcome Score (KOOS) Pain, Activity Daily Living (ADL) and QoL subscales (0–100; worst–best) were assessed by questionnaires prior and one year after surgery. Multivariable regression analyses were performed to determine associations between knee joint instability, pain, activity limitations and quality of life, adjusted for potential confounders including age, sex, comorbidities, physical activity and preoperative frailty.

Results: 908 patients were included of which 649 patients (72%) reported preoperative knee joint instability (mean age 67 years (SD8.6), 453 females (70%)) and 187 patients (21%) postoperative knee joint instability. Preoperative knee joint instability was associated with preoperative KOOS Pain (B-7.2;95% CI-10.9–3.5) and ADL (B3.8;95% CI-7.5–0.09), but not QoL (B-0.4;95% CI-2.1–1.2). In addition, postoperative knee joint instability was associated with postoperative KOOS Pain (B-13.5;95% CI-17.0–10.0), ADL (B-15.1;95% CI-18.4–11.8) and QoL (B-11.0;95% CI-13.5–8.5). Among the patients with preoperative self-reported knee joint instability, 165 patients (25%) retained knee instability and among the patients with no preoperative self-reported knee joint instability, 22 (8%) developed knee instability one year after surgery. After adjusting for baseline scores and potential confounders, retained knee joint instability was associated with postoperative KOOS Pain (B-19.6;95% CI-30.9–8.3), ADL (B-16.5;95% CI-27.0–5.9) and QoL (B-13.0;95% CI-17.9–8.1).

Conclusions: In usual care, knee joint instability is prevalent one year after TKA (21%). Reported knee joint instability is associated with more pain, worse physical function (pre- and postoperatively) and worse QoL postoperatively. Besides, retained knee joint instability was associated with worse pain, physical function and QoL. This emphasizes the importance of further research into the genesis of pre- and postoperative knee joint instability.

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SAT0506 EARLY POSTOPERATIVE IDENTIFICATION OF PATIENTS AT RISK FOR UNFAVOURABLE LONG-TERM OUTCOMES

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Background: Identification of patients who benefit from Total Hip or Knee Arthroplasty (THA or TKA) is necessary to indicate the need for surgery. This seems difficult as 20% of all patients report unfavourable outcomes. To provide better treatment options for patients with unfavourable outcomes, they should be identified at an early stage after surgery.

Objectives: I To investigate the prevalence of four trajectories in THA and TKA patients for both pain and function separately: (1) Patients with favourable initial and long-term outcomes, (2) patients with favourable initial but unfavourable long-term outcomes, (3) patients with unfavourable initial and favourable long-term outcomes and (4) patients with unfavourable initial and long-term outcomes. II To determine if long-term outcomes in all patients and in patient groups stratified by initial outcome (favourable/unfavourable) can be predicted on the basis of pre- and early postoperative variables.

Methods: Prospective, multicentre, observational study including consecutive patients undergoing primary THA and TKA (Longitudinal Leiden Orthopaedics and Outcomes of Osteoarthritis Study (LOAS)). Measurements were done preoperatively and at 6 and 12 months. Pain and function were assessed with the Hip Disability/ Knee injury and Osteoarthritis Outcome Scores (HOOS or KOOS) Pain and Activity Daily Living (ADL) subscales (score range 0–100). In addition, preoperative variables (sex, age, comorbidities) and early postoperative complications (reoperations or readmissions) were gathered by questionnaire. Scores of the Pain and ADL subscales above and below 70 were defined as favourable and unfavourable outcomes, whereas initial and long-term outcomes were defined as 6 months and 12 months after surgery, respectively. First the prevalence's of the trajectories were determined. Secondly, multivariable logistic regression analysis were done to examine if preoperative variables, postoperative complications and initial outcomes predicted long-term pain and function outcomes. Identical analyses were performed in the patients with favourable and unfavourable initial outcomes separately.

Results: 972 THA and 892 TKA patients were included. With respect to pain, the prevalence of trajectories 1, 2, 3 and 4 were 79% (n=740), 5% (n=47), 7% (n=63) and 9% (n=88) in THA and 75% (n=606), 4% (n=33), 9% (n=71) and 12% (n=93) for TKA. With respect to function, the prevalence's were 74% (n=696), 6% (n=53), 7% (n=63) and 14% (n=131) for THA and 72% (n=624), 5% (n=49), 9% (n=78) and 14% (n=119) for TKA, respectively. Moreover, one-third of the patients with initial unfavourable pain or function outcomes attained favourable long-term

outcomes. Overall, only the initial postoperative HOOS/KOOS pain and function predicted long-term outcomes (Table 1).

Table 1. Multivariable associations of preoperative or early postoperative pain or function outcomes with long-term pain or function outcomes

	Early postoperative associations with long-term outcomes in all patients		Early postoperative associations with long-term outcomes in patients with unfavourable early outcomes		Early postoperative associations with long-term outcomes in patients with favourable early outcomes	
THA	Pain N=151, ADL N=194	OR, 95% CI	Pain N=88, ADL N=131	OR, 95% CI	Pain N=63, ADL N=63	OR, 95% CI
HOOS Pain*	1.10	1.08-1.12	1.06	1.01-1.11	1.12	1.06-1.17
HOOS ADL*	1.13	1.10-1.16	1.07	1.02-1.12	1.13	1.06-1.20
TKA	Pain N=221, ADL N=197	OR, 95% CI	Pain N=121, ADL N=119	OR, 95% CI	Pain N=100, ADL N=78	OR, 95% CI
KOOS Pain*	1.10	1.08-1.13	1.06	1.02-1.11	1.14	1.01-1.21
KOOS ADL*	1.11	1.08-1.13	1.06	1.02-1.10	1.12	1.06-1.18

*Included in the multivariable model were age, sex, comorbidities (musculoskeletal and non-musculoskeletal), postoperative complications and the HOOS/KOOS pain or ADL subscale.

THA or TKA = Total Hip or Knee Arthroplasty

ADL = Activity Daily Living

HOOS = Hip Disability and Outcomes of Osteoarthritis Score

KOOS = Knee Injury and Outcomes of Osteoarthritis Score

OR = Odds Ratio

CI = Confidence Interval

Conclusions: One-third of patients with unfavourable initial outcomes improved further after the first six months after surgery. More research into the recovery early after surgery may help to identify patients at risk for unfavourable outcomes and modify their course by appropriate interventions.

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SAT0507 OXYTOCINE IN OSTEOARTHRITIS: FROM IN VITRO TO IN VIVO

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Background: The relationship between oxytocine (OT) and osteoarthritis (OA) is poorly studied and remains unknown. However the subchondral bone is considered as a major player in osteoarthritis, and a protective effect of OT on bone mineralization is described in recent studies.

Objectives: The aim of our work was to investigate a possible link between OT and OA

Methods: we used three different approaches: i) In vitro using MSC (adipose and bone marrow derived stem cells) that were maintained as mono-layer (2D) or as pellets in three dimension (3D) in the absence or the presence of OT. RT-PCR, histological and immunohistochemical analysis were performed. ii) in vivo using a rat animal model developing OA upon anterior cruciate ligament transection (ACLT). Twenty female Wistar rats were divided in 2 groups: one group was sham operated whereas the second was ACL transected. Half of each group received either OT (1 mg/kg/day) injections or saline buffer. Histological analysis was performed on day 28. The severity of OA lesions was assessed on a scale adapted from Mankin's score at medial part of the femur. iii) Clinical analysis using a human cohort. Samples issued from a hand OA cohort (ADEM). 63 OA women have been included; men were excluded because of their low number. At baseline, all subjects benefited of OT and leptin circulating levels measurements and hand X rays (Scoring systems including Kelgren and Lawrence and Verbruggen scores). The control group consists in subjects of the same age range without osteoporosis, OA or inflammatory disease.

Results: OT treatment of differentiating MSCs for 21 days induced a significant increase of aggrecan, Col X and COMP mRNA levels without variation of Col 1a. Immunostaining experiments showed an improvement of Sox9 and Col II expression in the presence of OT. The histological analysis of rat knee showed no differences in the severity of lesions between the different ACLT groups. The characteristics of the women cohorts is as follow: 63 OA women age = 65 (+/-11), Body Mass Index (BMI) = 24 (+/-4), OT=1.4 (+/-2) and 19 control women age=63 (+/-10), BMI=26 (+/-5), OT=6.5 (+/-7). The multivariate analysis adjusted for age, BMI and leptin levels, showed a significant lower level of OT in hand OA women (p=0.002, β =3.4). In univariate analysis, there was no relationship between OT blood levels and the severity of OA (Verbruggen: p=0.7, KL: p=0.2), Joint Space Narrowing (p=0.2) and osteophytes (p=0.1).

Conclusions: Our study shows an anabolic effect of OT on chondrogenesis and that OT circulating levels was significantly lower in OA patients. OT might represents an interesting player in the pathophysiology of osteoarthritis and further studies will shed some light on its mechanism of action.

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