detected in chondrogenic pellets and secreted by the differentiating MSCs. Finally, high levels of IL16 were detected in osteoarthritic cartilage.

Conclusions: We hypothesise that differentiation of MSCs initially involves hypermethylation to facilitate the rapid down regulatation of genes involved in self-renewal or alternative differentiation pathways. Epigenetic mechanisms also represent an important aspect of control to ensure the sequential and temporal expression of critical genes throughout the differentiation process. IL16, previously associated with synovial fibroblasts from rheumatoid joints was identified as a novel factor in chondrogenesis.

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NEUROMUSCULAR EXERCISE IMPROVES FUNCTIONAL PERFORMANCE IN PATIENTS WITH SEVERE HIP OSTEOARTHRITIS

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Purpose: Exercise is regarded a cornerstone in the treatment of mild to moderate osteoarthritis (OA). However, little is known of the effects in patients with advanced and end-stage OA. The purpose was to evaluate the effect of neuromuscular exercise in patients with severe hip OA.

Methods: *Design*. Randomized controlled trial (Clinicaltrials.gov identifier: NCT01003756). 84 patients, 51% female, mean age 68.6±7.8 years, BMI 28.7±4.7 scheduled for total hip replacement at Svendborg Community Hospital, Odense University Hospital, Denmark were included. *Intervention*. Participants were randomized to an eight-week neuromuscular exercise (NEMEX-TJR) intervention or care-as-usual (verbal and written preoperative information). Intervention was supervised and offered twice a week with each session lasting one hour. The program is considered feasible and safe in this patient group and previously described in detail. Assessments were carried out at baseline and within one week after the intervention. *Outcomes*. Functional performance: 20-m walk at maximal pace and 5 repeated chair stands timed. Muscle power: Unilateral multi-joint leg extension power and unilateral single-joint knee extension power evaluated with a leg extension press (Nottingham Power Rig, Nottingham University, Nottingham, UK) and a seated knee extension machine (Oemmebi, Moglia, Italy) adapted with a linear encoder (MuscleLab Power, Ergotest Technology, Langesund, Norway), respectively.

Results: On average the intervention group attended 13±4 sessions (Table 1). In favor of the intervention group, the between-group difference was significant for 20-m walk (2.2 seconds, p = 0.009), chair stands (1.7 seconds, p = 0.022) and leg extension for the non operated leg (.17 W/kg, p = 0.049) (Table 2).

Table 1. Baseline characteristics of study participants

	Exercise intervention	Care-as-usual
Scheduled for operation – no.	43	41
Female sex – no. (%)	22 (51)	21 (51)
Age – yr	68.7 [66.1;71.3]	68.6 [66.3;70.8]
BMI – kg m^{-2}	28.5 [27.3;29.7]	28.8 [27.1;30.5]
Exercise sessions – no.	13 [12.2;14.7]	–

Table 2. Baseline values and change over time (mean ± SD)

Outcome measure	Baseline		Change			
	Exercise intervention	Care-as-usual	Exercise intervention	Care-as-usual	Between-group mean difference	p-value
Muscle power (W kg^{-1})						
Multi-joint leg extension						
Non operated	1.28 [1.11;1.45]	1.33 [1.12;1.54]	0.22 [0.09;0.35]	0.05 [−.05;0.16]	0.17	0.049
Operated	1.02 [0.85;1.20]	1.09 [0.9;1.3]	0.07 [−0.07;0.20]	−0.05 [−0.18;0.08]	0.12	0.200
Single-joint knee extension						
Non operated	0.82 [0.67;0.96]	0.81 [0.65;0.97]	0.10 [0.05;0.16]	−0.01 [−0.14;0.11]	0.12	0.091
Operated	0.59 [0.47;0.72	0.58 [0.42;0.74	0.08 [0.01;0.14]	0.10 [−0.07;0.27]	0.03	0.761
Functional performance (s)						
Chair stands	13.1 [11.5;14.7]	13.4 [11.9;14.9]	−2.7 [−3.9;-1.4]	−0.5 [−1.6;0.7]	2.2	0.009
20-m max pace	15.2 [13.6;16.8]	15.6 [14.1;17.1]	−1.0 [−1.8;-.1]	0.7 [−0.5;1.9]	1.7	0.022

Conclusion: Eight weeks neuromuscular exercise according to the NEMEX-TJR program improves functional performance and leg extension power in patients with severe OA of the hip joint.

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TIME TO TOTAL HIP REPLACEMENT SURGERY AFTER SUPERVISED EXERCISE AND PATIENT EDUCATION IN PATIENTS WITH HIP OSTEOARTHRITIS. A RANDOMIZED INTERVENTION STUDY WITH BETWEEN 3.5 AND 6 YEARS FOLLOW UP

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Purpose: The purpose of the study was to evaluate time to total hip replacement (THR) surgery in patients with hip osteoarthritis going through both a supervised exercise program and patient education (SE+PE) compared to patients going through patient education only (PE).

Methods: One hundred and nine patients were included in the study between April 2005 and October 2007. Inclusion criteria were age 40–80 years, hip pain for three months or more, radiographically verified hip osteoarthritis (Danielson's criteria), and Harris Hip Score between 60–95 points, i.e. their impairments were not severe enough for considering THR at time of inclusion. All patients initially had three sessions of patient education. After completing the education program baseline assessments were conducted, and the patients were then randomized to 1) a 12 week supervised exercise program (SE+PE, n = 55), or 2) no further treatment (PE, n = 54). Both groups were recommended to follow the information giving during the patient education. The SE+PE group performed exercises 2–3 times weekly supervised by a physical therapist. The exercises consisted of strength training, functional exercises, and flexibility exercises.

Between April 12th and May 3rd 2011, 3.5 to 6 years after inclusion, all patients were contacted by telephone and information on whether and when THR surgery had been performed were collected. Survival analysis (Kaplan-Maier) were used to assess time to THR surgery in both groups. Group differences were tested by the Log Rank test.

Results: Twelve patients (11%) did not respond at latest follow-up (April/May 2011). Six of these patients had previously informed us that they had gone through THR surgery and at what time, and the remaining six patients were censored.

In total, 53 (48.6%) patients went through THR surgery within the follow-up time, 22 (40.0%) in the SE+PE group and 31 (57.4%) in the PE group. Median time to THR surgery was 1953 days (95% confidence interval (CI): 1634, 2272) and 1260 days (95% CI: 850, 1670) in the PE group. Cumulative survival without THR surgery after 6 years was 41.4% in the SE+PE group and 25.4% in the SE group (Figure 1, p = 0.034).

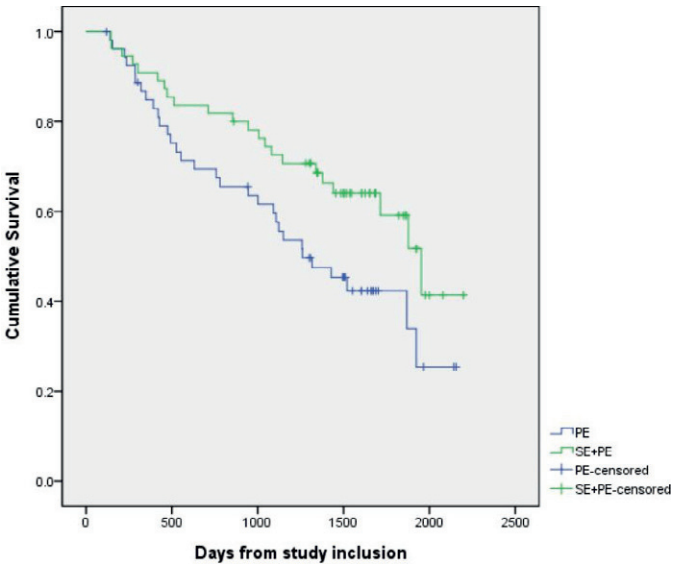

Fig. 1. Kaplan–Meier plot. Cumulative survival (without THR surgery) in the SE+PE group (green line) and the PE group (blue line). Censored data is marked at each line.

There were no significant differences between the groups at baseline in any patient characteristics or baseline assessments, including age, gender, minimal joint space, Harris Hip Score and self reported pain and function.

Conclusions: Cumulative survival without THR surgery were significantly higher for patients going through a both a supervised exercise program and patient education compared to patients going through patient education only, despite the fact that there were no significant differences in baseline characteristics between the two groups. The findings of this study suggest that supervised exercises in addition to patient education may postpone the need for THR surgery in patients with hip osteoarthritis.

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WALKING LOADING AT THE KNEE PREDICTS MRI-DERIVED CARTILAGE THICKNESS CHANGES IN MEDIAL COMPARTMENT KNEE OSTEOARTHRITIS

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Purpose: Knee osteoarthritis (OA) occurs in a substantial portion of the population over the age of 50. However, there is limited information on the underlying causes of OA and the reasons why the rate of disease progression varies between patients. In medial compartment knee OA, the peak knee adduction moment has been reported to predict disease progression as evaluated by radiographic JSW. However, mechanistic interpretation of radiographic measures of cartilage thinning is limited, and it is difficult to distinguish between femoral and tibial cartilage loss as well as assess if changes occur in specific walking load-bearing regions of the knee joint. Magnetic resonance (MR) imaging allows the investigation of specific regional changes in cartilage. We tested the hypothesis that baseline knee loading during gait predicts local MRI-derived cartilage loss in the medial compartment in patients with knee OA at a five year follow-up. Further, we hypothesized that increases in KAM over 5 years lead to focal increased cartilage loss.

Methods: Fourteen medial compartment OA knees (6 male, 8 female; age: 64.2±8.2 yrs) with an average baseline Kellgren-Lawrence grade of 2 were tested twice using MRI and gait analysis, with an average time between testing of 55 months following written consent in accordance with the Institutional Review Board. MR images were acquired with a 1.5T scanner (General Electric) using a 3D spoiled gradient-echo sequence in the sagittal plane. Images were manually segmented and 3D cartilage thickness maps were created. For local thickness analysis, the weight-bearing medial femoral cartilage was divided into three sub-regions: external, central, and internal. Similarly, the medial tibia cartilage was divided in five sub-regions: central, anterior, external, posterior, and internal. Subjects performed 3 walking trials at a self-selected normal speed in their personal shoes. Kinematic and kinetic data were captured using a 10-camera optoelectronic motion capture system (Qualisys), and the first peak knee adduction moment was calculated using inverse dynamics. Linear regression was used to test for a correlation between changes in cartilage thickness and joint loading. The level of significance was set at <0.05, with trends defined as <0.1.

Table 1. Correlation coefficients for associations between cartilage thinning and peak KAM

	Medial weight-bearing femur				Medial tibia					
	External	Central	Internal	Total	Central	Anterior	External	Posterior	Internal	Total
Baseline KAM										
R	-0.636	-0.514	0.158	-0.499	-0.487	-0.286	-0.189	-0.560	-0.247	-0.426
P-value	0.01	0.06	0.59	0.07	0.08	0.32	0.52	0.04	0.39	0.13
ΔKAM										
R	-0.602	-0.74	0.129	-0.630	-0.297	-0.455	-0.435	-0.254	-0.038	-0.335
P-value	0.02	0.00	0.66	0.02	0.30	0.10	0.12	0.38	0.90	0.24

Results: At the five-year follow-up, baseline peak KAM significantly predicted cartilage thinning in the medial femoral external region (P = 0.01), with trends towards correlations for the medial central (P = 0.06) and total medial (P = 0.07) weight-bearing regions (Table 1). Only one significant association between the baseline peak KAM and thinning was seen on the medial tibia posterior region (P = 0.04), with a trend for the central medial tibia (P = 0.08). When the change in adduction moment (ΔKAM) was considered there was a broader range of regions on the medial femur where cartilage thickness changes over 5 years were related to changes in KAM. An increase in ΔKAM was significantly associated with an increase in thinning for the external, central, and total weight-bearing medial femur (P = 0.02, 0.002, and 0.02, respectively). No significant associations were seen on the medial tibia.

Conclusions: These results suggest that over 5 years baseline KAM can predict OA progression, and suggest that the effect of the KAM on cartilage thinning may be region dependent, with more associations found on the medial weight-bearing femur. Further, an increased loss of cartilage thickness is associated with an increase in dynamic joint loading over 5 years, which may further accelerate the rate of OA progression, and suggest the KAM should be reduced to slow disease progression.

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GENOME WIDE EXPRESSION PROFILING OF NORMAL, RHEUMATOID AND OSTEOARTHRITIC SYNOVIAL STEM CELLS

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Purpose: Within synovial joints, damage to the articular cartilage surface is thought to be irreversible in part due to the lack of stem cells within the cartilage. Interestingly, however, the synovial lining of the joint and the synovial fluid itself contains adult stem cells similar in behaviour and potential to mesenchymal stem cells (MSCs). *In vitro* these synovial MSCs (sMSCs) display increased chondrogenic potential compared to fat and bone marrow MSCs, and are indeed present in normal joints, with greater numbers of stem cells within arthritic joints. While it does not appear that these cells are able to affect repair within individuals with osteoarthritis (OA) or rheumatoid arthritis (RA), there is growing evidence from animal models that sMSCs and/or synovial tissue can contribute to articular cartilage repair *in vivo*.

Methods: In our current study, synovial fluid MSCs were isolated and characterized from normal, OA and RA knee joints diagnosed using the American College of Rheumatology Standards and analyzed at the genome-wide expression levels using micro-array technology. Nine genes of interest were identified for further study and validated using qPCR in 5 normal, 5 OA and 5 RA individuals. Furthermore, sMSCs were analyzed from five patients with early osteoarthritis identified through arthroscopic examination and were found to show similar expression patterns to sMSCs collected from advanced OA and RA joints.

Results: A number of genes were found to be differentially regulated between normal, OA and RA sMSCs (Figure 1). Cartilage oligomeric matrix protein (COMP), Cathepsin K (CTSK), Iterleukin-1 receptor type I (IL1R1), Stromelysin-1 (MMP3), SPARC-related modular calcium-binding protein 2 (SMOC2), Osteopontin (SPP1), Substance-P receptor (TACR1), Thrombospondin-2 (THBS2) and Tenascin-X (TNXB) expression levels were all significantly different between normal and arthritic sMSCs as well as early OA sMSCs.

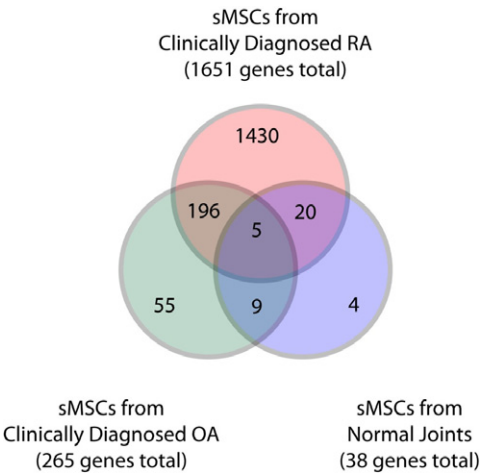

Fig. 1. Representation of differentially regulated genes in sMSC population. sMSCs from normal, OA and RA synovial fluid (n = 2 each) were subjected to microarray analysis. All genes shown are significantly expressed p > 0.05.

Conclusions: The resulting data strongly suggests that the synovial stem cell biology is altered during arthritis at the genome wide expression level, even in OA cases, where joint space narrowing is not