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CHANGES IN PROPRIOCEPTIVE WEIGHTING IN WOMEN WITH KNEE OSTEOARTHRITIS DURING QUIET STANDING COMPARED TO HEALTHY CONTROLS

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Purpose: Knee osteoarthritis (OA) is highly prevalent in people above the age of 60 and is associated with pain, muscle weakness, and proprioceptive deficits at the knee joint. Muscle-tendon vibration has been used in different populations such as elderly and patients with low back pain, to assess the use of proprioceptive information from different body parts in postural control. One recent study by Shanahan et al, used muscle vibration to assess the proprioceptive weighting in a group of subjects with knee osteoarthritis (KL grade 3 or 4). To the best of our knowledge this has not been done in patients with early medial knee OA. Therefore, to better understand the progression of proprioceptive impairments with the natural course of knee OA, we aimed to investigate the proprioceptive reweighting in group of subjects with early OA according to the classification criteria of Luyten (so beginning joint degeneration on MRI), and compare them to their healthy peers and patients with established OA.
Methods: Standing was challenged by vibrating ankle muscles (i.e. tibialis anterior (TA) and triceps surae (TS)) and knee musculature (vastus medialis (VM)) in 27 women with early OA, 24 with established OA, and 27 healthy controls. Two muscle vibrators were utilized bilaterally with a frequency of 70 Hz and amplitude of approximately 0.5 mm. These specific vibration characteristics are used to induce a maximum illusory motion. Each trial lasted for 45 seconds, where muscle-tendon vibration was applied during the middle 15 seconds. Center of pressure (CoP) displacement was recorded using a force plate (1000 Hz). CoP position was calculated and averaged over the first 15 s of the trial (pre-vibration), during the 15 s of vibration, and after the cessation of vibration (post-vibration). The absolute difference in mean CoP position before and during vibration was then calculated as the response to muscle vibration. Also, the postural recovery from muscle vibration was defined and calculated as the absolute difference in mean CoP position during and after vibration. The ratio between the response to vibration of the VM and TS (TS/ (TS + VM) and VM and TA (TA/ (TA + VM)) was calculated as measure of proprioceptive weighting.
Results: Both early and established OA groups showed significantly different postural control strategies compared to healthy controls in favor of ankle muscle proprioceptive control (ratio closer to 1) (TS/VM= 0.87, P =0.033 and TS/VM= 0.89, P =0.015, respectively).
Vibration of triceps surae resulted in a significantly larger effect on CoP both at response and recovery, in the early (PResponse=0.023 and PRecovery<0.001) and established (PResponse=0.006 and PRecovery=0.003) OA groups compared to the healthy controls.
Conclusions: The results from this study suggest that knee OA might lead to down weighting of the proprioceptive information from knee muscles. In conclusion, Subjects with knee OA seem to rely more on ankle proprioceptive input, as previously found in elderly, which suggests alterations in postural control that might be present early in the disease process.

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KRÜPPEL-LIKE FACTORS (KLFS), NOVEL TRANSCRIPTIONAL REGULATORS OF ARTICULAR CHONDROCYTES THAT ARE ABNORMALLY EXPRESSED IN OSTEOARTHRITIC CARTILAGE

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Purpose: Krüppel-like factors (Klfs) are known to play key roles in cell cycle regulation, definition of cell fate and regulation of terminal differentiation. There is no information on expression and function of Klfs in cartilage. The objectives of this study were to analyze expression of Klfs in normal and OA cartilage and study their role in regulating chondrocyte functions.
Methods: Klf expression in normal and OA human cartilage and in developing mouse limb buds was examined by next generation RNA sequencing and qPCR. Klf4 function in normal human chondrocytes and TC28 immortalized chondrocytes was analyzed by gene overexpression and knock down. Overexpression of Klf4 mutants and reporter constructs were used to determine critical motifs for Klf regulation of gene expression.
Results: Next generation RNA sequencing showed that Klf2, 4, 5, 9, 10 and 15 are significantly suppressed in OA cartilage. Quantitative real time PCR for mouse limb buds showed significantly increased Klf2, 4 and 5 expression from E11.5 to E15.5. Over expression-based screening in the immortalized human chondrocyte cell line TC28 revealed that only Klf4 strongly enhanced Col2A1 and Acan gene expression. Conversely, knockdown of Klf4 resulted in suppression of Col2A1 and Acan genes in human primary chondrocytes. Luciferase reporter assays showed that Klf4 binds to consensus sequences of Col2A1 and Acan promoters and activates their expression. ChIP-qPCR for Col2A1 promoter and Co-IP study revealed that Klf4 could interact with Sox9 directly. Klf4 C-terminus, which contains three tandem zinc fingers, which are critical for this interaction are required for activation of the target genes. Finally, we demonstrated that induction of Klf4 expression could induce Col2A1 and Acan expression in various cell types including dedifferentiated chondrocytes, and the magnitude of upregulation of the target genes was attenuated by reduction of Sox9 expression.
Conclusions: These results are the first to show that Klf factors have a tissue specific expression in articular cartilage and that OA is associated with dysregulated expression of several Klfs. Among the Klfs, Klf4 expression pattern is most closely linked with chondrogenic markers. Klf4 promotes expression of chondrocyte specific genes, in part through direct interaction with Sox9. Collectively, these findings implicate abnormal expression of Klfs as a novel mechanism of abnormal chondrocyte differentiation and activation in OA.

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THE ONSET OF KNEE OSTEOARTHRITIS AFTER ANTERIOR CRUCIATE LIGAMENT SURGERY IS ASSOCIATED WITH EARLY UNLOADING FOLLOWED BY AN EXTENDED PERIOD OF NORMAL LOADING

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Purpose: Previous work from our group has shown that subjects who exhibit radiographic signs of premature knee osteoarthritis (OA) 5 years after unilateral anterior cruciate ligament reconstruction (ACLR) also have reduced loading in the involved knee after injury and 6 months post-surgery. We have also reported that the loading difference between involved vs. uninvolved knees normalizes 1-2 years post-surgery. Many cross-sectional studies and few prospective studies support the idea that OA progression is associated with increased knee loads. However, there is limited data addressing knee joint loading during the period over which OA develops. Our subject cohort with OA at 5 years provides a unique opportunity to characterize the time course of loading associated with OA onset. In this abstract, we present preliminary results contrasting the time course of loading between individuals who develop premature knee OA within 5 years after ACLR, versus subjects who do not develop knee OA.
Methods: The data set included 9 subjects (4 females, 5 males, Age: 32 ± 12 years) for whom we had loading data as well as radiographs 5 years after ACLR. Weight-bearing anterior-posterior radiographs, taken 5 years after ACLR, were graded using the Kellgren-Lawrence (K-L) scale. A K-L grade equal or greater than 2 in the medial compartment was defined to be indicative of OA. 3 out of 9 subjects showed signs of OA 5 years after ACLR. Prior to injury, all subjects were actively involved in cutting and pivoting activities and none of the subjects had knee OA. Subjects with repairable meniscal tears, full-thickness chondral defects > 1 cm2 and symptomatic grade III injury to other knee ligaments were excluded from the study. All surgeries were performed using either an allograft or a hamstring autograft. All subjects were tested following 10