molecular chaperone activity (clustering). Interestingly, other proteomic studies have identified clustering and CILP-1 as being upregulated in early human OA. These biomarkers may be involved in early repair responses in cartilage and thus may be useful for the detection of early changes in OA.

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A41 EPHB4 RECEPTOR ACTIVATION BY ITS SPECIFIC LIGAND EPHRIN B2 INDUCED A REDUCED REMODELING PROCESS IN HUMAN SUBCHONDRAL BONE OSTEOBLASTS

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Purpose: Ephrin is well documented in the literature for its functions in the nervous and cardiovascular systems. However, it has recently been shown that the interaction of the EphB4 receptor with its specific ligand ephrin B2 could be implicated in the physiological regulation of bone homeostasis. Osteoarthritis (OA), although characterized by cartilage breakdown and inflammation of the synovial membrane, also demonstrates important changes in the subchondral bone. Recent studies have shown that an abnormal remodeling process of this tissue is intimately involved in the genesis of OA. We recently classified human OA subchondral bone osteoblasts into two subgroups according to their low (L) or high (H) POE2 levels. Further data has demonstrated that the L-OA showed bone pro-resorption activities and the H-OA pro-formation properties. In this study we determined the presence, level and modulation of EphB4 receptors on each of these subgroups. Further, we investigated the modulation of EphB4 receptors and the effect of their activation by ephrin B2 on OA osteoblasts.

Methods: The in situ presence of EphB4 receptors in the subchondral bone was determined by immunohistochemistry. The EphB4 receptor expression level, modulation upon treatment with osteotropic factors, and effect of activation by ephrin B2 on bone catabolic mediators were determined using real-time PCR. The ephrin B2-activated EphB4 receptor effect on the bone resorption activity was also determined using a coculture system of differentiated human PBMC and human subchondral bone osteoblasts. The intra-cellular signaling pathways employed by the EphB4 receptor activation were investigated by specific ELISA.

Results: Data showed that EphB4 receptors were present in the human subchondral bone osteoblasts and osteocytes. A significant increase in EphB4 receptor expression level was found in the L-OA osteoblasts compared to the normal (p < 0.0002) and the H-OA (p < 0.0007). However, there was no difference between the normal and the H-OA. EphB4 receptor levels in the L-OA osteoblasts were significantly up-regulated by PGE2 and IL-17. Interestingly, ephrin B2, PGE2 and IL-17 significantly inhibited the bone resorption activity in L-OA osteoblasts. EphB4 activation by ephrin B2 significantly inhibited the expression level of the pro-inflammatory cytokines IL-1β and IL-6, the metalloproteases MMP-1, MMP-9 and MMP-13, as well as RANKL. The factors MMP-2 and OPG were not modulated. The EphB4 receptor activation significantly reduced the PI3K/Akt pathway, but had no significant effect on the MAP kinases.

Conclusions: This study, for the first time, provides evidence that EphB4 receptor activation by ephrin B2 in human OA subchondral bone could impact abnormal metabolism in this tissue by inhibiting resorption factors and their activities. The differential level of EphB4 receptors in the L-OA and H-OA subchondral bone osteoblasts also indicates that these cells have a different pathobiological stage. Data from this study will help to light that ephrin B2 could be targeted as a specific therapeutic approach in the development of a disease modifying OA drug, as this factor could exert a protective effect on OA articular tissue structural changes.

A42 A GENOME-WIDE ASSOCIATION STUDY REVEALS A NOVEL LOCUS FOR HAND OSTEOARTHRITIS

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Purpose: Although a significant genetic effect on hand osteoarthritis (OA) has been reported, confirmed replicated genetic factors have not yet been identified. The aim of this study, therefore, was to identify specific genetic polymorphisms for hand OA by means of the genome-wide association study (GWAS) in Caucasian population.

Methods: A three stage approach was utilized. First, we conducted a GWAS implementing 317,818 SNPs across the entire genome in 651 women of the North European origin from the TwinsUK registry. Next, we tested the top 100 SNPs identified in our GWAS in the Rotterdam cohort, consisting of 1438 men and women aged over 50. In the final stage, we searched for confirmation of the association between the OA and SNPs that showed the most significant association results in the second stage. To this aim we used additional independent population-based sample – the Chingford Study, including 671 British women. All participants in the study had their both hands X-rayed, and 15 joints on each hand (DIP,PIP,MCP, and first CMC) were scored for OA, using Kellgren-Lawrence (KL) system. The total KL score adjusted for age (and sex) was used in the analysis.

Results: We identified replicated evidence of an association between the SNP which is located in chromosome16p13 and hand OA. The minor allele with a frequency of 32% significantly decreased (OR=0.68, 95% CI 0.49-0.95) the risk of OA. This finding was confirmed in all three cohorts combined. When we categorized the participants of the TwinsUK and the Chingford study into two groups: people who had at least two joints of hands affected, defined by KL ≥ 2, vs individuals who didn’t have any hand’s joints affected, the minor allele was associated with a 33% reduction of risk in the development of hand OA (p = 0.0002). The risk was further reduced to 41% if the cases are defined as at least three joints affected (p = 0.00001).

Conclusions: This genome-wide scan identified a significant association between OA and a novel locus which has a potential role in transcriptional regulation of calcitonin. This finding provides insight into previously unknown genetic mechanisms in the development of hand OA.

A43 THE RELATIONSHIP OF DENUDED SUBCHONDRAL BONE AREA TO KNEE PAIN SEVERITY AND INCIDENT FREQUENT KNEE PAIN

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Purpose: Subchondral bone has attracted attention as a potential source of pain in knee OA in part because of its intimate relationship to overlying cartilage and its load bearing function. With full thickness cartilage defects, exposed bone may be more likely to generate joint pain during contact and weightbearing activity. We hypothesized that (1) increased %denuded bone in OA knees is associated with increased pain and (2) greater %denuded bone predicts incident frequent knee pain.

Methods: All participants had knee OA by definite osteophytes. Axial double oblique coronal SPGR sequences were acquired on a 1.5T or a 3T scanner. Images were processed with proprietary software (Chondrometrics). Manual segmentation by trained readers was used to compute total area of subchondral bone, cartilage surface area, and cartilage-covered and denuded areas of bone for the medial tibia, lateral tibia, weightbearing medial and lateral femur, and patella. Pain severity was assessed with a knee-specific 100 mm VAS for pain in the past week. Frequent knee pain was defined as pain in or around the knee for most days in the past month. To test hypothesis 1, we used median quantile regression to determine the increase in median pain score per (2) greater%denuded bone predicts incident frequent knee pain.

Results: Of the 176 knees, 53 developed frequent knee pain over the next 2 years. Analyses were adjusted for age, gender, BMI, K/L grade, and bone edema score.

Purpose: Subchondral bone area to knee pain severity and incident frequent knee pain

Frequent knee pain was defined as pain in or around the knee for most days in the past month. To test hypothesis 1, we used median quantile regression to determine the increase in median pain score per (2) greater %denuded bone predicts incident frequent knee pain.

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The effect of chondroitin sulfate on indirect comparison of clinical efficacy across patients with osteoarthritis: A meta-analysis with mixed treatment comparisons

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Purpose: There have been numerous of systematic reviews of interventions designed to diminish pain and improve function for patients with OA, but the comparable effectiveness of such interventions is unclear. To assess the clinical efficacy of physiotherapeutic (PT) modalities and interventions available in library of Cochrane reviews, on the pain and disability in patients with osteoarthritis (OA), applying data from published systematic Cochrane reviews of RCTs would be a useful method.

Methods: The Cochrane Library was searched for Cochrane reviews considering patients with OA and different physiotherapeutic interventions with the aim of reducing pain, and disability. A meta-regression analysis was applied, for the mixed treatment comparisons, applying the individual study’s standardized mean difference (SMD) as outcome measure, for pain and disability, respectively. The statistical random-effects model was based on a restricted maximum likelihood (REML), mixed-effects model procedure with intervention as fixed- and trial as random-factor, respectively. The within study variance was considered known for each published RCT, based on the explicit SD’s presented in each of the original Cochrane reviews. A negative SMD favors the intervention on trial.

Results: The search with “osteoarthritis” in the title resulted in 35 reviews. Reasons for exclusion was protocols (K=12), pharmacological treatments and surgery (K=15), withdrawn (K=1) and 1 study compared two different kinds of treatment (K=1). Thus, 6 Systematic Cochrane Reviews were included in the meta-regression model (patients included, N=3,016): Lateral wedged insoles (LWI, pain K=1; disability k=1), transcutaneous electrical nerve stimulation (TENS, pain K=6, disability K=0), thermotherapy (THT, pain K=1; disability k=1), and ultrasonic therapy (UST, pain K=1; disability k=0). According to the published efficacy on pain; data are presented in descending efficacy (SMD) order with the corresponding p-value: EMF (SMD: −1.13, p < 0.001); EMF, cold (SMD: −0.81, p < 0.001); TENS (SMD: −0.43, p < 0.001); TENS (SMD: −0.40, p < 0.001); TENS (SMD: −0.40, p < 0.001); TENS (SMD: −0.40, p < 0.001).

Conclusions: Based on this mixed treatment comparison, we provide quantitative evidence-based efficacy ranking of the PT interventions currently available as an updated Cochrane review. Based on the reported pain and disability reduction, it is highly evident (p < 0.0001) that exercise therapy does benefit the patient; although not necessarily with the largest magnitude of efficacy. Of the other therapies tested, both EMF and TENS showed a relevant effect size of moderate statistical significance (SMD: −0.43, p < 0.001); TENS (SMD: −0.40, p < 0.001); TENS (SMD: −0.40, p < 0.001); TENS (SMD: −0.40, p < 0.001); TENS (SMD: −0.40, p < 0.001); TENS (SMD: −0.40, p < 0.001).

The present indirect-comparison provide the clinician a view of the modalities to choose, accordingly LWI, UST might not be effective in the treatment of osteoarthritis.

Tai Chi is effective in treating knee osteoarthritis: A randomized controlled trial

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Purpose: Knee osteoarthritis (KOA) is a major cause of pain and functional impairment among elders and has no medical remedy. The