tendon homeostasis such as expression of important extracellular matrix components (collagen type I, elastin), matrix degrading enzymes (MMP-1, -3) and to evaluate tenocyte inflammatory response by investigation of pro-inflammatory (TNF-alpha, Il-1beta) and immunoregulatory (Il-6) cytokine as well as suppressors of cytokine signalling (SOCS1, SOCS3) expression.
Methods: Cultured primary human tenocytes were investigated for endogen Il-10 and Il-10 receptor-1 (Il-10R1) expression as a prerequisite for Il-10 signalling using RTD PCR and immunohistichemistry. Serum starved tenocytes were treated with recombinant human Il-6, Il-10, TNF-alpha or combinations of TNF-alpha with Il-6 and Il-10 (10 or 50 ng/mL, 24 h, 48 h). Expression of type I collagen, elastin, MMP-1, -3, TNF-alpha, Il-1beta, Il-6, SOCS1 and SOCS3 was studied by RTD PCR, immunohistochemistry or by western blot analysis.
Results: In the presence of TNF-alpha human tenocytes expressed Il-10 and the Il-10 specific Il-10R1. Il-6 stimulated tenocyte collagen type I expression at the protein level, but had obviously no effect on elastin expression. TNF-alpha amplified slightly elastin expression, but decreased type I collagen deposition.
TNF-alpha activated the tenocytes to highly up-regulate their gene expression for matrix degrading enzymes (MMP-1, -3) as well as pro-inflammatory (TNF-alpha, Il-1beta) and immunoregulatory cytokines (Il-6). The treatment of tenocytes with recombinant Il-6 and Il-10 alone had no major effect on their cytokine expression, the co-treatment with Il-6 or Il-10 and TNF-alpha inhibited only slightly the expression of TNF-alpha, Il-1beta and Il-6 in response to TNF-alpha. TNF-alpha stimulation, but not the treatment with Il-6 or Il-10 augmented SOCS1, whereas SOCS3 gene expression was only up-regulated by Il-6 in tenocytes.
Conclusions: Tenocytes are able to express the immunoregulatory cytokine Il-10 and its specific Il-10R1. However, the function of Il-10 in tendon remains mainly unclear: Il-10 might play a role under inflammatory conditions in tendon.
The results of the study indicate inflammatory, catabolic, but also distinct anabolic effects of TNF-alpha which strongly activates the tenocytes to produce several pro-inflammatory and immunoregulatory cytokines, matrix degrading enzymes, suppresses collagen type I deposition but, however, increases elastin expression. The observed induction of SOCS1 by TNF-alpha was not sufficient to inhibit the TNF-alpha up-regulation mediated by TNF-alpha. The multiple roles of TNF-alpha in tendon remodelling and the modulatory influence of Il-6 and Il-10 under inflammatory conditions have to be further analysed.

Pain: Clinical

465 MODERATE TO SEVERE OSTEOARTHRITIS, BUT NO PAIN

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Purpose: It is known that there is discordance between pathological evidence of osteoarthritis (OA), seen with radiographs, and clinical symptoms and signs. Suggestions are made that this is particularly true for the less severe grades of OA and that in more severe grades of OA pain is more common. Still there are people with Kellgren and Lawrence (K&L) grade 3 or 4 of OA in hip and knee that do not have pain in hip or knee. To better understand the absence of pain in people with moderate or severe OA, it is necessary to find out determinants related to pain in people with moderate to severe radiological OA. In this study, we determine which determinants explain the pain in hip or knee in people with Kellgren and Lawrence grade 3 or 4 in knee or hip.
Methods: Participants in this study were participants of the Rotterdam study, which included from 1990 onwards all inhabitants of 55 years and older living in Ommoord, a district in Rotterdam. The aim of the Rotterdam study was to investigate determinants of disease occurrence and progression of chronic disabling diseases. All participants have had an interview, an examination and x-rays.
We identified all participants who hade moderate to severe OA (K&L grade 3 or 4) in hip or knee. Univariate logistic regression was used to analyze the association between pain and moderate to severe OA of knee or hip. Patient characteristics and variables for co-morbidity, health status, depression, widespread pain, other symptoms of osteoarthritis, familial OA, and bilaterality were tested.
Results: There were 7983 men and women participating in the Rotterdam Study, of which 6450 visited the research centre for baseline examination. Of 3035 participants the x-ray of the knees and 3320 x-rays of the hips were scored with K&L. We identified 164 participants with moderate to severe OA (K&L grade 3 or 4), 99 participants had pain in knee or hip and 65 participants had no pain in knee or hip. In univeriate logistic regression analysis pain in knee or hip is associated with morning stiffness (OR 3.9, p = 0.000), bilateral knee OA grade 3 or 4 (OR = 3.0, p = 0.038), health complaint (OR = 3.0, p = 0.001).
Conclusions: Morning stiffness, bilateral knee OA, and health complains are indicators for having pain with moderate to severe OA. These determinants are all indicators of disease and cannot explain the absence of pain with moderate to severe OA. Maybe an explanation for the absence in pain can be found in genetic research. Another limitation of this study is that a lot of possible determinants are not measured in this cohort, for example physical activity. The sample size of this study was very small and there were only 65 cases.

466 LATERAL JOINT SPACE NARROWING ON RADIOGRAPHS PREDICTS PAIN PROGRESSION IN KNEE OSTEOARTHRITIS PATIENTS: APPLICATION OF FULLY AUTOMATIC KOACAD SYSTEM TO OAI PUBLIC DATA

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Purpose: To establish an objective and accurate quantification method of the structural severity of knee osteoarthritis (OA), we have developed a computer program KOACAD (knee OA computer-aided diagnosis) which for the first time has realized a fully automatic measurement of major OA parameters on plain knee radiographs (OA&C 2008). The present study sought to identify radiographic factors that predict the future progression of pain in knee OA patients by applying the KOACAD system to the NIH Osteoarthritis Initiative (OAI) public data.
Methods: This study used the progression subcohort data in the OAI (public-use dataset 0.C.1), since all subjects in the subcohort were knee OA patients with frequent knee symptoms and radiographic knee OA. From 814 subjects, 722 without knee surgery (292 men and 430 women, average 61.8 yrs.) who completed the WOMAC scores at baseline and 24-month follow-up surveys were enrolled. More than 20% increase of the WOMAC knee pain score during the follow-up period was defined as the progression of knee pain. On plain anteroposterior radiographs at the baseline, we measured the six major OA parameters: medial and lateral joint space area (JSA), medial and lateral minimum joint space width (mJSW), osteophyte area, and tibiofemoral angle (TFA), using the KOACAD system. The non-paired t-test was used to examine the difference of age, gender, body mass index (BMI), and the KOACAD parameters between the groups with and without the knee pain progression. Furthermore, odds ratio (OR) and the associated 95% confidence interval (CI) were determined using logistic regression analysis after adjustment for age, gender and BMI. A p-value of <0.05 for analysis of safety variables was considered significant.
Results: The mean WOMAC pain score was 4.1 (range: 0−19) at the baseline and 3.8 (0−18) at the 24-month follow-up, and the mean change was −0.3 (−13±10). In the overall 722 patients, 46 (14 men and 32 women) showed the knee pain progression. There was no significant difference of age, gender, and BMI between the groups with and without the pain progression (46 vs. 676). Among the KOACAD parameters at the baseline, medial JSA (93.6±5.7 for progression vs. 92.3±1.4 mm^2 for non-progression; mean±S.D.), lateral JSA (102.8±6.8 vs. 113.5±1.7 mm^2), medial mJSW (2.6±0.2 vs. 2.8±0.1 mm), osteophyte area (1.1±1.0 vs. 2.7±0.2 mm^2), and TFA (176.3±0.2 vs. 176.5±0.6 degree) were not significantly different between the two groups; however, lateral mJSW (3.3±0.5 vs. 4.3±0.1 mm) was significantly lower in the group with the knee pain progression (p = 0.0083). Logistic regression analysis after adjustment for age, gender and BMI confirmed that low lateral mJSW was associated with the pain progression (OR = 1.24, 95% CI = 1.04−1.46). The association was stronger in women (OR = 1.32, 95% CI = 1.05−1.68) than in men (OR = 1.13, 95% CI = 0.94−1.41).
Conclusions: Utilizing the KOACAD system and the OAI public data, we have found that lateral joint space narrowing on plain radiographs, but not medial joint space narrowing, osteophytosis or knee angulation, can be a predictive parameter of the pain progression in knee OA patients. Interestingly, our previous cross-sectional study using the KOACAD showed significant association of medial joint space narrowing, but not lateral joint space narrowing, with the presence of knee pain in a normal population-based cohort, implicating a distinct etiology between the incidence and

progression of knee pain. The KOACAD system will be useful for objective evaluation of the disease severity in daily clinical practice, just as bone mineral density is in osteoporosis.

467 NEUROPATHIC PAIN SYMPTOM MEASURES STRIKE A NERVE IN OSTEOARTHRITIS

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Purpose: Pain is the most common, disabling symptom for people with Osteoarthritis (OA). Cumulative data suggests dysfunctional pain processing by the central nervous system, called central sensitization (CS), contributes to pain in OA. CS can be associated with the neuropathic pain (NP) symptom profile including burning, electric-shock like sensations, and sensitivity to light touch. Improved understanding of pain mechanisms in OA, including development of "clinically feasible" tools to identify individuals likely to have CS would facilitate development of novel mechanism-based pain therapies. This ongoing study is assessing (1) NP symptoms in subjects with symptomatic knee OA, using a NP questionnaire modified for use in OA, the modified painDETECT (mPD-Q), and the Self-completed Leeds Assessment of Neuropathic Symptoms and Signs pain scale (S-LANSS), which has been validated in other chronic pain populations; (2) pain intensity, using the Von Korff Chronic Pain Grade Scale (CPG) and, (3) co-morbid chronic pain and neurological conditions.
Methods: Eligible study subjects are members of an existing population-based OA cohort with chronic symptomatic knee OA defined by pain, discomfort and/or stiffness in the knee(s) on most days for $\geqslant$ 3 months. A standardized questionnaire was mailed to 268 cohort members to date, to assess (1) pain quality for each knee using the mPD-Q, scored -1 to 38; and the S-LANSS, scored 0−24; (2) pain intensity, using the CPG, scored 0–100; and (3) co-morbid conditions. Mean, median, and standard deviation (SD) were evaluated for questionnaire scores. The proportion of knee OA cohort participants with mPD-Q and S-LANSS scores in the 'NP range' (mPD-Q score $\geqslant$19, S-LANSS score $\geqslant$12) was calculated using a 95% confidence interval. Pearson correlations between mPD-Q and other questionnaire scores (SLANSS and CPG) were examined.
Results: To date, 129 (48%) questionnaires have been returned. Thirty-two (29%) responders reported no chronic knee pain. Among 92 (71%) responders with chronic knee pain, 73 had chronic right and 63 had chronic left knee pain. Mean (SD) mPD-Q scores were the same, 12 (7), for right and left knees. Mean (SD) S-LANSS scores were 8 (8) for right knees and 7 (7) for left knees. According to cut-points identified in other pain populations, the proportion (95% CI) of study subjects with scores in the 'NP range' on the mPD-Q was 0.21 (0.12−0.32) for right knees and 0.17 (0.08−0.28) for left knees; on the S-LANSS was 0.31 (0.20−0.42) for the right knees and 0.25 (0.14−0.36) for left knees. The mPD-Q scores had a moderate to high correlation with the S-LANSS scores for right ($r = 0.68$) and left knees ($r = 0.73$). The mPD-Q scores had a moderate correlation with CPG pain intensity scores for right ($r = 0.61$) and left ($r = 0.65$) knees. The following factors did not explain the variability seen in mPD-Q scores: presence of diabetes, another chronic pain condition, a co-morbid neurological condition.
Conclusions: In a population-based cohort with chronic knee OA, almost a quarter of subjects with painful knee OA scored in the 'NP range' on both of the measures assessed. This subgroup of patients may benefit from further evaluation for NP likely due to CS and consideration of NP medications. Further validation work on the mPD-Q is ongoing.

468 FURTHER VALIDATION OF OARSI-OMERACT INTERMITTENT AND CONSTANT OSTEOARTHRITIS PAIN (ICOAP) MEASURE

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Purpose: To further assess the construct validity of ICOAP, a new osteoarthritis (OA) pain measure.
Methods: The new measure, ICOAP, is comprised of 5 items assessing 'constant' hip or knee pain and 6 items assessing 'intermittent' hip or knee pain; item response options are on a 4-point scale from 'not at all' to 'extremely'. Subscale and total scores are standardized to 0 to 100, where higher scores indicate worse pain. The ICOAP was administered by phone to an established community cohort aged 55+ years with moderate to severe hip and/or knee OA. All subjects completed both the hip and knee versions of the ICOAP, regardless of which joints were painful at the time. Participants also completed other measures of arthritis pain and disability (WOMAC pain, function and stiffness subscales; McGill pain intensity scale, and the limitation dimension of the Late Life Function and Disability Instrument), the Profile of Mood States-Brief (POMS) fatigue/inertia scale, the SF-36 general health perception scale, the CES-D scale for depressed mood, the Lubben Social Network Scale, and the Pain Catastrophizing Scale. Summary descriptive statistics were calculated for all scale scores. Spearman's rho correlation coefficients were calculated to assess the relationship between ICOAP Hip and Knee subscale and total scores with each of the other measures. T-tests were used to compare means ICOAP scores for men versus women.
Results: The mean age of the 659 participants was 77.6 years (58.7 to 97.9), 77.4% were female and 23.7% had < high school education; 631 had complete data for ICOAP Hip and 608 for ICOAP Knee. Mean score (SD) for the hip was 26.8 (SD 25.0) and 18.0 (SD 26.8) for intermittent and constant pain, respectively. For the knee, mean intermittent and constant pain scores were 30.9 (SD 23.3) and 16.0 (SD 26.5), respectively. Women had higher intermittent and total ICOAP pain scores than men (hip and knee results similar, $p < 0.05$ for all). Within individuals, intermittent and constant pain scores were only modestly correlated ($r = 0.29$ for the knee; $r = 0.46$ for the hip, $p < 0.0001$ for both) and their strength of association with other measures differed (e.g. correlation with pain catastrophizing score: intermittent pain $r = 0.27$ versus constant pain $r = 0.39$). For the hip, measures of coping, fatigue, mood and physical functioning were more strongly related to constant than to intermittent pain. For the knee, the reverse was generally true, with stronger correlations being associated with intermittent knee pain scores. ICOAP score correlations with WOMAC pain scores ranged from 0.39 (hips; ICOAP intermittent pain) to 0.65 (knees; ICOAP total pain). Higher scores for both intermittent and constant pain were associated with lower general health status, higher scores on other pain and disability measures, higher scores for depression, fatigue and pain catastrophizing, and lower scores for social support.
Conclusions: Our results provide further evidence of the ICOAP as a valid tool for evaluation of pain in hip and knee OA and supports use of the two subscale scores for intermittent and constant pain independently as distinct and important domains of OA pain.

469 C-REACTIVE PROTEIN LEVELS ARE ASSOCIATED WITH OA-RELATED KNEE PAIN IN WOMEN

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Purpose: Four previous studies ($n = 1675$) have shown that C-Reactive Protein (CRP) levels are associated with (progression of) knee osteoarthritis (KOA). At this moment, there are only three studies ($n = 968$) published, examining the relationship between CRP levels and joint complaints or disability. In this population-based study, we analyzed the association between CRP levels and KOA-related knee pain and the relationship between CRP levels, body mass index (BMI) and KOA since it is still not clear whether BMI plays a role as a confounder or as effect mediator in this model.
Methods: In total, 1655 women from the Rotterdam Study had data on radiographic knee OA, age, BMI and CRP levels. High-sensitivity CRP measurements were performed using rate near-infrared particle immunoassay. For all statistical analysis, log-transformed CRP values were used. KOA was defined as a Kellgren/Lawrence score $\geqslant$2 in one or both knees. Knee pain was defined as having pain in the right or left knee during the last month or the past five years.
Results: Women with knee OA had 30% higher CRP levels compared to women without KOA ($p = 8 \times 10^{-7}$), but after adjustment for age and BMI this association disappeared ($p = 0.3$). We next stratified our data according to BMI, to investigate the role of BMI as an effect modifier. We observed that women with a BMI < 27.0 kg/m^2 and with KOA had 34% higher levels of CRP compared to women without KOA ($p = 0.004$ after adjustment for age and co-morbidity). Importantly, this association was absent in women with a BMI > 27.0 kg/m^2 ($p = 0.63$). CRP levels were borderline significant associated with an increased risk of knee pain in our study ($p = 0.053$ after adjustment for age and BMI). This effect was only visible in women with radiographic KOA (27% higher CRP levels, $p = 0.03$ after adjustment for age and BMI) and not in women without KOA ($p = 0.43$).