induced a 10 fold or greater upregulation of several proinflammatory genes, including cytokines Il-1β, Il-6, Il-12, Il-17, and mediators, COX-2, iNOS, MMP-1, MMP-3, MMP-4, MMP-7, MMP-9, MMP-13. However, the genes were expressed at negligible to very low density in unstimulated control chondrocytes. Cluster analysis of chondrocytic genes in response to low/physiological DTF showed that these signals markedly regulate genes associated with chondrocyte growth and proliferation, BMP-2, SOX-9, GDF-5, TGF-β, BMP-4, BMP-7, IGF-1, IGF-2; genes associated with cartilage extracellular matrix, proteoglycans and collagens, apoptosis, cell cycle associated genes, signaling cascades, MAP kinases, NF-kB cascade, SMADs, and intracellular structural proteins (actin, tubulin, vimentin, etc), adhesion molecules. 

Conclusions: The results demonstrate that mechanical signals dynamically cause complex magnitude-dependent gene regulation. Certain gene clusters or representative genes are distinct, whereas others overlap in response to low or high magnitudes of DTF. This differential magnitude-dependent gene regulation may play a key role to ultimately allow the remarkable and beneficial/detrimental effects of mechanical signals that are realized at cartilage level. 

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**THE ETIOLOGY OF KASHIN-BECK DISEASE (KBD): THE EFFECTS OF FUNGAL MYCOTOXINS ON CHONDROCYTE AND CARTILAGE METABOLISM**

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Purpose: KBD is an endemic osteoarthropathy which is mainly characterised by the degeneration and necrosis of hyaline articular cartilage. At present the etiology and pathogenesis of KBD is unclear. The aim of this study was to investigate the expression of proteoglycan, hyaluronic acid (HA) receptor CD44 and other factors that regulate cartilage metabolism using the chondrocytes and tissue grafts cultured under in vitro conditions that mimic some of the etiological factors that are thought to be involved in the pathogenesis of KBD.

Methods: Different concentrations of mycotoxins suspected as etiological factors causing KBD; i.e. nivalenol (NIV), deoxynivalenol (DON), T-2 toxin, butenolide (BUT) and moniliformin (MON), and Selenium (Se) which is thought to abrogate KBD pathology, were added at physiological concentrations to cultured chondrocytes and artificial cartilage grafts in vitro to establish models of cartilage degeneration and necrosis similar to that found with KBD. In addition, cartilage tissue and blood samples were collected from KBD patients. RT-PCR was used to detect mRNA expression of CD44, HA synthese (HAS), aggrecan, aggrecanase, matrix metalloproteinases (MMP) and tissue inhibitor of metalloproteinases (TIMPS). Corresponding protein expression was determined using Western blot analyses. Immunohistochemistry was used to study the effects of the mycotoxins on cartilage extracellular matrix metabolism; i.e. neuproteases for matrix proteinase degradation (BC-3/BC-13 & BC-4/BC-14) and CD44. ELISA were used to quantify II-1α, TNF-α, MMPs, soluble CD44 and HA levels in the culture media and KBD patient serum.

Results: A decrease of chondrocyte density and a gradual increase in chondrocyte degeneration and necrosis were observed with the increase of mycotoxin concentrations. Se addition partially alleviated this cartilage degeneration, but did not change the overall trend of degenerative changes. mRNA expression of aggrecan, TIMP-1 and -3 decreased whilst that of CD44, HAS, aggrecanase-1 and -2, and MMPs increased in chondrocytes cultured with the mycotoxins; Se addition showed some changes that extracellular matrix staining for cartilage aggrecan became weak and non-uniform but after Se addition this matrix staining improved. The expression of aggrecan specific degradation neuproteases in cartilage matrix increased in the presence of the mycotoxins, and this was reduced after Se addition. The expression of CD44 on the chondrocyte cell membrane decreased and that in matrix increased in the presence of the toxins. The levels of glucuronic acid, soluble CD44 and HA in cell culture media increased gradually with the increase of mycotoxin concentration. After Se addition, the levels of glucuronic acid showed a decrease, but that of soluble CD44 levels did not change. The levels of II-1α and TNF-α in the culture media of the toxin groups were higher than control groups.

Conclusions: These in vitro studies have exposed chondrocyte and cartilage graft cultures to conditions of mycotoxin exposure that mimic those believed to be involved in the etiology of KBD patient pathology. Our results indicate that many of the pathogenic and degradation changes observed in KBD patients are expressed in this model in vitro culture systems including the abrogation of some of these effects by adding Selenium.

**Clinical Aspects/Outcomes**

**TOPICAL TREATMENT OF PAINFUL OSTEOARTHRITIS WITH COMFREY ROOT EXTRACT OINTMENT: RESULTS OF A DOUBLE-BLIND RCT**

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Purpose: Topical treatment of painful muscular and joint complaints with comfrey root ointment has often been questioned in terms of efficacy. However, several randomised controlled trials (RCT) impressively showed the efficacy and safety in blunt injuries and muscle pain of the back. Most recent data confirmed even superiority versus topical diclofenac in acute unilateral ankle sprains. However, more clinical trials were demanded to prove the efficacy in further painful disorders, like osteoarthritis. The aim of this study was to investigate the clinical value of the ointment in the treatment of patients with painful osteoarthritis of the knee.

Methods: This randomised, double-blind, placebo-controlled study was performed in accordance with the Declaration of Helsinki/Hong Kong 1989/Somerset 1996 as well as ICH-GCP Guidelines. 220 patients (153 women, 67 men, mean age: 57.9 years) daily received 6 g (3 x 2 g) of either an active ointment (Kytta-Salbe®), containing comfrey root fluid extract 1:2, 35.0 g) or a corresponding placebo, for 21 days. The active ointment is available in Germany and Switzerland as a Pharmacy (P) OTC drug and in the UK on the General sales list (GSL). Pain, stiffness and functional impairment are the important symptoms sought to relieve. Therefore, the primary target variable was the Visual Analog Scale (VAS) sum score of pain at rest and pain on movement. Secondary target variable was the Western Ontario and McMaster Universities (WOMAC) score.

All patients met the criteria of the American College of Rheumatology. Baseline characteristics were compared and a statistical analysis was performed and verified that there was no statistical difference between the verum and the placebo group.

Results: In the course of the study, the VAS sum score (primary target variable) decreased by 51.6 mm (54.7%) in the active therapy group and by 10.1 mm (10.7%) in the placebo group. The mean group difference of 41.5 mm or 44.0% points was significant (p < 0.001).

The WOMAC percentage sum score (secondary target variable) also decreased strongly. At the end of the study, a reduction by 60.4 mm (58.0%) was observed in the active therapy group and by 14.7 mm (14.1%) in the placebo group. The mean group difference of 45.7 mm or 43.9% points was significant (p < 0.001).

With regard to the exploratory target variables SF-36 (quality of life), angle measurement (knee mobility), CGI (clinical global impression) and global efficacy assessment by investigator and patient, again a significant superiority was demonstrated (p < 0.001, respectively) for the phytotherapeutic agent versus placebo. 7 patients of the active therapy group were rated as, no longer requiring treatment.

Conclusions: The verum reduced the symptoms of osteoarthritis of the knee significantly. The therapy lead to reduction of pain, improved knee mobility and better quality of life. Therefore, the present clinical trial has demonstrated that the topical application of a comfrey root extract is a sensible and safe treatment option for patients with painful osteoarthritis.

**THE PROGNOSTIC VALUE OF CLINICAL CLASSIFICATION CRITERIA OF KNEE OSTEOARTHRITIS IN GENERAL PRACTICE**


Purpose: To assess the prognostic value of the clinical ACR classification criteria of knee osteoarthritis (OA) in general practice.

Methods: Patients consulting for non-traumatic knee complaints in general practice aged >35 years were enrolled in the study. At baseline and during one year follow-up knee complaints and function was assessed by 3-monthly questionnaires. A physical examination was performed at baseline and after one year follow-up. The prognostic value of fulfilling the
clinical ACR criteria of knee OA on persisting knee complaints, increase of disability (WOMAC function score), and increase of absence of work through illness after one year follow-up was assessed.

Results: 659 patients were included in the study of which 480 (87.4%) were available for follow-up. The studied population contained 236 (49.2%) women, mean age 53.6 (sd 11.3), mean BMI 27.1 (sd 4.2), 288 (60.0%) patients had payed employment (>8 hours/week), and 292 (60.8%) patients fulfilled the ACR clinical criteria of knee OA. After one year follow-up, 236 (49.2%) patients reported persisting knee complaints, 84 (17.5%) reported an increase of disability, and 5 (1%) patients reported an increase of absence of work through illness. There was no association between fulfilling the ACR clinical criteria of knee OA and persisting knee complaints (OR 1.15; 95% CI 0.80, 1.67), increase of disability (OR 1.05; 95% CI 0.43, 2.58), and increase of absence of work through illness (OR 0.97; 95% CI 0.16, 5.83) after one year follow-up.

Conclusions: The ACR clinical classification criteria of knee OA have no prognostic value in adult patients with non-traumatic knee complaints in general practice during the period of one year follow-up.

### 246 USING GROUP-BASED TRAJECTORY MODELING TO IDENTIFY PATTERNS OF JOINT SPACE NARROWING IN KNEE OA OVER TWO YEARS

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Purpose: Change in joint mean joint space width (JSW) is currently the gold standard for assessing disease progression in knee osteoarthritis (OA) clinical trials. Although probability plots and histograms have been used to examine change at the individual level, longitudinal modeling methods that use all data collected are available to look at pattern clusters of change over time.

Methods: We performed secondary data analyses of 622 men and women with medial compartment knee OA enrolled in the placebo arm of a 2 yr multi-national study of the effects of a bisphosphonate on OA symptoms and radiographic progression. At baseline, participants had x-rays with 2−4 mm JSW in the medial compartment of the knee. Minimal JSW of the medial compartment was measured from fluoroscopically-positioned radiographs obtained at baseline, 12 and 24 months. Group-based trajectory modeling was used to identify distinctive groups of individuals with similar trajectories of JSW change over two years taking into account sex, age and body mass index (BMI).

Results: The optimal number of groups identified from the trajectory analysis was seven. Group assignment was associated with gender, age and BMI but not geographic site (North America vs. European Union). JSW stability over 2 years was observed in 4 groups representing the most common trajectory (70%), irrespective of initial JSW. Three groups showed statistically significant (p <0.01) narrowing of JSW: two groups with the narrowest joint space at baseline (2.1 and 2.3 mm JSW), comprised 8% and 20% of the sample respectively and showed an average narrowing of 0.7 mm. and 0.2 mm. A small group (2%) had a mean decrease of 2.1 mm. As compared to participants in the group with the largest JSW at baseline (mean 3.7 mm; 22% of sample), participants in the group with the most JSW narrowing were more likely to be female, while those with more moderate narrowing were significantly older with a higher BMI.

Conclusions: In the medial compartment of the knee, minimal JSW remains stable over 2 years in most men and women, with further narrowing that was greater than measurement error observed in only 10%. Longitudinal modeling of JSW data can be used to study patterns of change over time.

### 247 CORRELATION BETWEEN PATIENT SELF ASSESSMENT OF TREATMENT EFFICACY (PATE) AND OTHER OUTCOME VARIABLES. RESULTS OF A STANDARDIZED FOLLOW-UP IN PATIENTS TREATED WITH INTRA-ARTICULAR INJECTION OF HYALURONIC ACID FOR HIP OSTEOARTHRITIS

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Purpose: To determine the validity of patient self assessment of treatment efficacy (PATE) compared to other usually used outcome variables.

Methods: Standardized follow-up (FU). Patients: Forty patients suffering from hip OA treated by a single intra-articular injection of non-animal-stabilized hyaluronic acid (NASHA) in the painful hip under fluoroscopy. Evaluation: PATE, patient global assessment (PGA) and walking pain (WP) on a 100 mm visual analogue scale, WOMAC index, Lequesne index at each visit. Statistics: Last observation carried forward. Treatment was considered as effective when patients reported PATE >50 mm (PATE50+). PATE at last visit of FU was compared to the usually used outcome variables, obtained from PGA, WOMAC and WP: OMERACT-OARSI response criteria, Minimal Clinically Important Improvement (MCII), Patient Acceptable Symptom State (PASS) using Mann-Whitney test

Results: Thirty four patients were assessable (mean FU 159 days): 22 were PATE50 + (mean PATE [SD] = 77.1 [12.7] mm) and 12 not (10.7 [18.0] mm). PATE50 was correlated with PASS (p=0.01), MCII (p=0.017) and OMERACT-OARSI responders (p=0.017). PASS and OMERACT-OARSI were also correlated (p=0.001) as well as OMERACT-OARSI and MCII (p=0.005). In contrast there was no correlation between PASS and MCII (p=0.21). PATE was strongly correlated with Lequesne index reduction (p<0.001) and walking pain decrease (p=0.002). PATE at month 1 was also highly predictive of the efficacy at month 6 (P=0.003).

Conclusions: This study showed that PATE could be useful, as a clinical outcome variable, to easily assess the efficacy of viscosupplementation in hip OA in routine practice. Evaluation of the value of these surrogate outcome variable needs to be conducted in larger samples of subjects and in OA oral medication treatment.

### 248 RELATION BETWEEN ALIGNMENT AND PAIN IN PATIENTS SURGICALLY TREATED FOR MEDIAL KNEE OSTEOARTHRITIS BY HIGH TIBIAL OSTEOTOMY. A ONE YEAR FOLLOW-UP STUDY

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Purpose: The relation of lower extremity alignment and knee pain is unclear. High tibial osteotomy, a treatment option for unicompartmental knee osteoarthritis (OA), alters load from the affected to the unaffected compartment of the knee by correcting malalignment. This surgical procedure thus offers the possibility to study the cross-sectional and longitudinal relation of alignment to pain. The aim of this study was to (1) the preoperative relation of alignment to preoperative pain and (2) the relation of change in alignment with surgery to change in pain preoperatively compared to at one year postoperatively in patients operated on for knee OA by high tibial osteotomy using the hemicallotasis technique.

Methods: 82 patients (80% men) mean age 62 years (range, 35–69) with varus alignment having tibial osteotomy by the hemicallotasis technique (HCO) for unicompartmental medial knee OA were consecutively included. Alignment was assessed by the Hip-Knee-Ankle (HKA) angle from radiographic including the hip and ankle joints. The HKA angle was defined as a line from the center of the femoral head to the midpoint of the tibia and another line from this midpoint to the center of the talus surface of the ankle joint. The medial angle between these lines is the HKA angle (varus <180 degrees). Pain was measured by the subscale Pain (0–100, worst to best scale) of the Knee injury and Osteoarthritis Outcome Score (KOOS) preoperatively and at one...