induced a 10 fold or greater upregulation of several proinflammatory genes, including cytokines Il-1b, Il-6, Il-8, Il-12, Il-17, and mediators, COX-2, iNOS, MMP-1, MMP-3, MMP-4, MMP-7, MMP-9, MMP-13. However, these 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; grouped differently 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.  www.NIH AT00646, AR04878, NIDCR DE15399.

THE ETIOLOGY OF KASHIN-BECK DISEASE (KBD): THE PROGNOSTIC VALUE OF CLINICAL CLASSIFICATION

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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 the mRNA expression of CD44, HA synthase (HAS), aggrecan, aggreganases, 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., neoptelopes for matrix proteinase degradation (BC-3/BC-13 & BC-4/BC-14) and CD44. ELISAs were used to quantify Il-1β, 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 cartilage degeneration and necrosis were observed with the increase of mycotoxin concentrations. Addition of nivalenol to the culture medium decreased strongly. At the end of the study, a reduction by 60.4mm (58.0%) was observed in the active therapy group and by 14.7mm (14.1%) in the placebo group. The mean group difference of 45.7mm (58.0%) was observed in the active therapy group and by 14.7mm (14.1%) in the placebo group. The mean group difference of 41.5mm 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 60.4mm (58.0%) was observed in the active therapy group and by 14.7mm (14.1%) in the placebo group. The mean group difference of 45.7mm or 43.9% points was significant (p<0.001).

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.

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 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: 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 6g (3×2g) of either an active ointment (Kytta-Salbe® f, containing comfrey root extract 1:2, 35.0g) or a corresponding placebo, for 21 days. The active ointment is available in Germany and Switzerland as a Pharmaceutical (P) OTC drug and in the UK on the General sales list (GSL). Pain, stiffness and functional impairment are the important symptoms patients seek 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 51.6mm (54.7%) in the active therapy group and by 10.1mm (10.7%) in the placebo group. The mean group difference of 41.5mm 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 60.4mm (58.0%) was observed in the active therapy group and by 14.7mm (14.1%) in the placebo group. The mean group difference of 45.7mm or 43.9% points was significant (p<0.001).

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