

## Research Abstracts:

glucosamine sulfate, vitamin D, boswellia, turmeric, l-glutamine, bromelain, cetyl myristoleate

### **Glucosamine long-term treatment and the progression of knee osteoarthritis: systematic review of randomized controlled trials**

**OBJECTIVE:** To investigate the structural and symptomatic efficacy and safety of glucosamine in knee osteoarthritis (OA). **DATA SOURCES:** Clinical trials of glucosamine were identified through electronic searches (MEDLINE, EMBASE, BIOSIS, EMB review, the Cochrane Library) using the key words glucosamine, osteoarthritis, degenerative joint disease, degenerative arthritis, osteoarthrosis, gonarthrosis, knee, disease progression, and clinical trial. The bibliographic databases were searched from their respective inception dates to August 2004. We also hand-searched reference lists of relevant articles. **STUDY SELECTION AND DATA EXTRACTION:** Studies were included if they were double-blind, randomized, controlled trials that evaluated oral glucosamine long-term treatment in knee OA; lasting at least one year; and reporting as outcome measures the symptom severity and disease progression as assessed by joint space narrowing. Two authors interpreted data independently. Disagreements were resolved through discussion. **DATA SYNTHESIS:** Glucosamine sulfate was more effective than placebo in delaying structural progression in knee OA. The risk of disease progression was reduced by 54% (pooled RR 0.46; 95% CI 0.28 to 0.73;  $p = 0.0011$ ). The number-needed-to-treat was 9 (95% CI 6 to 20). The pooled effect sizes for pain reduction and improvement in physical function were 0.41 (95% CI 0.21 to 0.60;  $p < 0.0001$ ) and 0.46 (95% CI 0.27 to 0.66;  $p < 0.0001$ ), respectively, in favor of glucosamine sulfate. Glucosamine sulfate caused no more adverse effects than placebo. **CONCLUSIONS:** The available evidence suggests that glucosamine sulfate may be effective and safe in delaying the progression and improving the symptoms of knee OA. Due to the sparse data on structural efficacy and safety, further studies are warranted. Poolsup N, Suthisisang C, Channark P, Kittikuluth W. *Ann Pharmacother*. 2005 Jun;39(6):1080-7.

### **Glucosamine sulfate reduces osteoarthritis progression in postmenopausal women with knee osteoarthritis: evidence from two 3-year studies**

**OBJECTIVE:** To investigate the effect of glucosamine sulfate on long-term symptoms and structure progression in postmenopausal women with knee osteoarthritis (OA). **DESIGN:** This study consisted of a preplanned combination of two three-year, randomized, placebo-controlled, prospective, independent studies evaluating the effect of glucosamine sulfate on symptoms and structure modification in OA and post-hoc analysis of the results obtained in postmenopausal women with knee OA. Minimal joint space width was assessed at baseline and after 3 years from standing anteroposterior knee radiographs. Symptoms were scored by the algo-functional WOMAC index at baseline and after 3 years. All primary statistical analyses were performed in intention-to-treat, comparing joint space width and WOMAC changes between groups by ANOVA. **RESULTS:** Of 414 participants randomized in the two studies, 319 were postmenopausal women. At baseline, glucosamine sulfate and placebo groups were comparable for demographic and disease characteristics, both in the general population and in the postmenopausal women subset. After 3 years, postmenopausal participants in the glucosamine sulfate group showed no joint space narrowing [joint space change of +0.003 mm (95% CI, -0.09 to 0.11)], whereas participants in the placebo group experienced a narrowing of -0.33 mm (95% CI, -0.44 to -0.22;  $P < 0.0001$  between the two groups). Percent changes after 3 years in the WOMAC index showed an improvement in the glucosamine sulfate group [-14.1% (95%, -22.2

to -5.9)] and a trend for worsening in the placebo group (5.4% (95% CI, -4.9 to 15.7) (P = 0.003 between the two groups). CONCLUSION: This analysis, focusing on a large cohort of postmenopausal women, demonstrated for the first time that a pharmacological intervention for OA has a disease-modifying effect in this particular population, the most frequently affected by knee OA. Bruyere O, Pavelka K, Rovati LC, et al. *Menopause*. 2004 Mar-Apr;11(2):138-43.

### **Vitamin D intake is inversely associated with rheumatoid arthritis: results from the Iowa Women's Health Study**

OBJECTIVE: Vitamin D is a potent regulator of calcium homeostasis and may have immunomodulatory effects. The influence of vitamin D on human autoimmune disease has not been well defined. The purpose of this study was to evaluate the association of dietary and supplemental vitamin D intake with rheumatoid arthritis (RA) incidence. METHODS: We analyzed data from a prospective cohort study of 29,368 women of ages 55-69 years without a history of RA at study baseline in 1986. Diet was ascertained using a self-administered, 127-item validated food frequency questionnaire that included supplemental vitamin D use. Risk ratios (RRs) and 95% confidence intervals (95% CIs) were estimated using Cox proportional hazards regression, adjusting for potential confounders. RESULTS: Through 11 years of followup, 152 cases of RA were validated against medical records. Greater intake (highest versus lowest tertile) of vitamin D was inversely associated with risk of RA (RR 0.67, 95% CI 0.44-1.00, P for trend = 0.05). Inverse associations were apparent for both dietary (RR 0.72, 95% CI 0.46-1.14, P for trend = 0.16) and supplemental (RR 0.66, 95% CI 0.43-1.00, P for trend = 0.03) vitamin D. No individual food item high in vitamin D content and/or calcium was strongly associated with RA risk, but a composite measure of milk products was suggestive of an inverse association with risk of RA (RR 0.66, 95% CI 0.42-1.01, P for trend = 0.06). CONCLUSION: Greater intake of vitamin D may be associated with a lower risk of RA in older women, although this finding is hypothesis generating. Merlino LA, Curtis J, Mikuls TR, et al. *Arthritis Rheum*. 2004 Jan;50(1):72-7.

### **1,25-Dihydroxyvitamin D3 as a natural regulator of human immune functions**

1,25-dihydroxyvitamin D3 (1,25-D3) modulates lymphocyte and macrophage functions in vitro. These effects are exerted through production of 1,25-D3 by antigen-presenting monocytes/macrophages (MO) and binding to vitamin D receptors expressed in MO and in activated, but not in resting T-lymphocytes. 1,25-D3 inhibits production of MO-derived cytokines such as interleukin-1 alpha, interleukin-6, and tumor necrosis factor alpha at the post-transcriptional level, most likely by reducing the half-life of specific mRNAs. The proliferation of T-cells and their release of cytokines such as IL-2 and interferon gamma are also suppressed by 1,25-D3, partly as a result of the reduced production of T-cell-activating cytokines (interleukin-1 alpha, tumor necrosis factor alpha), but also because of a direct effect on the T-cells. Although 1,25-D3 has no apparent effect on B-lymphocytes, the T-cell suppression indirectly inhibits antibody production by B-cells. The CD45R0+ subset of T-helper cells is relatively more sensitive than the CD45RA+ subset to the inhibitory effects of 1,25-D3. The CD45R0+ subset plays a key role in immune activation and in the pathogenesis of many autoimmune disease. 1,25-D3 acts as an important local regulator of T-cell functions and thus modulates several immunological effector functions. The actions of 1,25-D3 are distinct from those of commonly used immunosuppressants, and vitamin D3 analogs are therefore potentially useful as alternatives to conventional immunosuppressive therapies. Müller K, Bendtzen K. *J Investig Dermatol Symp Proc*. 1996 Apr;1(1):68-71.

### **Why is L-glutamine metabolism important to cells of the immune system in health, postinjury, surgery or infection?**

Glutamine is normally considered to be a nonessential amino acid. However, recent studies have provided evidence that glutamine may become "conditionally essential" during inflammatory conditions such as infection and injury. It is now well documented that under appropriate conditions, glutamine is essential for cell proliferation, that it can act as a respiratory fuel and that it can enhance the function of stimulated immune cells. Studies thus far have determined the effect of extracellular glutamine concentration on lymphocyte proliferation and cytokine production, macrophage phagocytic plus secretory activities and neutrophil bacterial killing. Other cells of the immune system remain to be studied. The high rate of glutamine utilization and its importance to the function of lymphocytes, macrophages and neutrophils have raised the question "why glutamine?" because these cells have access to a variety of metabolic fuels both in vivo and in vitro. I have attempted to answer this question in this article. Additionally, knowledge of the rate of utilization and the pathway of metabolism of glutamine by cells of the immune system raises some intriguing questions concerning therapeutic manipulation of utilization of this amino acid such that the proliferative, phagocytic and secretory capacities of cells of the defense system may be beneficially altered. Evidence to support the hypothesis that glutamine is beneficially immunomodulatory in animal models of infection and trauma, as well as trauma in humans, is provided. Newsholme P. *J Nutr.* 2001 Sep;131(9 Suppl):2515S-22S; discussion 2523S-4S.

### **Nonsteroidal anti-inflammatory agents differ in their ability to suppress NF-kappaB activation, inhibition of expression of cyclooxygenase-2 and cyclin D1, and abrogation of tumor cell proliferation**

Nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin have been shown to suppress transcription factor NF-kappaB, which controls the expression of genes such as cyclooxygenase (COX)-2 and cyclin D1, leading to inhibition of proliferation of tumor cells. There is no systematic study as to how these drugs differ in their ability to suppress NF-kappaB activation and NF-kappaB-regulated gene expression or cell proliferation. In the present study, we investigated the effect of almost a dozen different commonly used NSAIDs on tumor necrosis factor (TNF)-induced NF-kappaB activation and NF-kappaB-regulated gene products, and on cell proliferation. Dexamethasone, an anti-inflammatory steroid, was included for comparison with NSAIDs. As indicated by DNA binding, none of the drugs alone activated NF-kappaB. All compounds inhibited TNF-induced NF-kappaB activation, but with highly variable efficacy. The 50% inhibitory concentration required was 5.67, 3.49, 3.03, 1.25, 0.94, 0.60, 0.38, 0.084, 0.043, 0.027, 0.024, and 0.010 mM for aspirin, ibuprofen, sulindac, phenylbutazone, naproxen, indomethacin, diclofenac, resveratrol, curcumin, dexamethasone, celecoxib, and tamoxifen, respectively. All drugs inhibited I $\kappa$ B kinase and suppressed I $\kappa$ B degradation and NF-kappaB-regulated reporter gene expression. They also suppressed NF-kappaB-regulated COX-2 and cyclin D1 protein expression in a dose-dependent manner. All compounds inhibited the proliferation of tumor cells, with 50% inhibitory concentrations of 6.09, 1.12, 0.65, 0.49, 1.01, 0.19, 0.36, 0.012, 0.016, 0.047, 0.013, and 0.008 mM for aspirin, ibuprofen, sulindac, phenylbutazone, naproxen, indomethacin, diclofenac, resveratrol, curcumin, dexamethasone, celecoxib, and tamoxifen, respectively. Overall these results indicate that aspirin and ibuprofen are least potent, while resveratrol, curcumin, celecoxib, and tamoxifen are the most potent anti-inflammatory and antiproliferative agents of those we studied. Takada Y, Bhardwaj A, Potdar P, Aggarwal BB. *Oncogene.* 2004 Dec 9;23(57):9247-58.

### **Bromelain reduces mild acute knee pain and improves well-being in a dose-dependent fashion in an open study of otherwise healthy adults**

There is preliminary clinical evidence to support the contention that the anti-inflammatory and analgesic properties of bromelain help to reduce symptoms of osteo- and rheumatoid arthritis. However, there have been no controlled studies of its effects on joint health in healthy subjects who lack such diagnosis. The current study investigated the effects of bromelain on mild acute knee pain of less than 3 months duration in otherwise healthy adults. The study was an open, dose-ranging postal study in volunteers who had been recruited through newspaper and magazine articles. Two validated questionnaires (WOMAC knee health Index and the Psychological Well-Being Index) were completed at baseline and after one month's intervention with bromelain, randomly allocated to volunteers as either 200 mg or 400 mg per day. Seventy seven subjects completed the study. In both treatment groups, all WOMAC symptom dimension scores were significantly reduced compared with baseline, with reductions in the final battery (total symptom score) of 41 and 59% ( $P = 0.0001$  and  $<0.0001$ ) in the low and high dose groups respectively. In addition, improvements in total symptom score ( $P = 0.036$ ) and the stiffness ( $P = 0.026$ ) and physical function ( $P = 0.021$ ) dimensions were significantly greater in the high-dose (400 mg per day) compared with the low-dose group. Compared to baseline, overall psychological well-being was significantly improved in both groups after treatment ( $P = 0.015$  and  $P = 0.0003$  in the low and high dose groups respectively), and again, a significant dose-response relationship was observed. We conclude that bromelain may be effective in ameliorating physical symptoms and improving general well-being in otherwise healthy adults suffering from mild knee pain in a dose-dependant manner. Double blind, placebo-controlled studies are now warranted to confirm these results. Walker AF, Bundy R, Hicks SM, Middleton RW. *Phytomedicine*. 2002 Dec;9(8):681-6.

### **Efficacy and tolerability of Boswellia serrata extract in treatment of osteoarthritis of knee- -a randomized double blind placebo controlled trial**

Osteoarthritis is a common, chronic, progressive, skeletal, degenerative disorder, which commonly affects the knee joint. Boswellia serrata tree is commonly found in India. The therapeutic value of its gum (guggulu) has been known. It posses good anti-inflammatory, anti-arthritic and analgesic activity. A randomized double blind placebo controlled crossover study was conducted to assess the efficacy, safety and tolerability of Boswellia serrata Extract (BSE) in 30 patients of osteoarthritis of knee, 15 each receiving active drug or placebo for eight weeks. After the first intervention, washout was given and then the groups were crossed over to receive the opposite intervention for eight weeks. All patients receiving drug treatment reported decrease in knee pain, increased knee flexion and increased walking distance. The frequency of swelling in the knee joint was decreased. Radiologically there was no change. The observed differences between drug treated and placebo being statistically significant, are clinically relevant. BSE was well tolerated by the subjects except for minor gastrointestinal ADRs. BSE is recommended in the patients of osteoarthritis of the knee with possible therapeutic use in other arthritis. Kimmatkar N, Thawani V, Hingorani L, Khyani R. *Phytomedicine*. 2003 Jan;10(1):3-7.

### **Boswellic acids in chronic inflammatory diseases**

Oleogum resins from BOSWELLIA species are used in traditional medicine in India and African countries for the treatment of a variety of diseases. Animal experiments showed anti-inflammatory activity of the extract. The mechanism of this action is due to some boswellic acids.

It is different from that of NSAID and is related to components of the immune system. The most evident action is the inhibition of 5-lipoxygenase. However, other factors such as cytokines (interleukins and TNF-alpha) and the complement system are also candidates. Moreover, leukocyte elastase and oxygen radicals are targets. Clinical studies, so far with pilot character, suggest efficacy in some autoimmune diseases including rheumatoid arthritis, Crohn's disease, ulcerative colitis and bronchial asthma. Side effects are not severe when compared to modern drugs used for the treatment of these diseases. Ammon HP. *Planta Med.* 2006 Oct;72(12):1100-16.

### **Cetylated fatty acids improve knee function in patients with osteoarthritis**

**OBJECTIVE:** To determine the benefit of cetylated fatty acids (CFA) on knee range of motion and function in patients with osteoarthritis (OA). **METHODS:** Sixty-four patients with chronic knee OA were evaluated at baseline and at 30 and 68 days after consuming either placebo (vegetable oil; n = 31) or CFA (Celadrin; n = 33). Evaluations included physician assessment, knee range of motion with goniometry, and the Lequesne Algofunctional Index (LAI). **RESULTS:** After 68 days, patients treated with CFA exhibited significant ( $p < 0.001$ ) increase in knee flexion (10.1 degrees) compared to patients given placebo (1.1 degrees). Neither group reported improvement in knee extension. Patient responses to the LAI indicated a significant ( $p < 0.001$ ) shift towards functional improvement for the CFA group (-5.4 points) after 68 days compared to a modest improvement in the placebo group (-2.1 points). **CONCLUSION:** Compared to placebo, CFA provides an improvement in knee range of motion and overall function in patients with OA of the knee. CFA may be an alternative to the use of nonsteroidal antiinflammatory drugs for the treatment of OA. Hesslink R Jr, Armstrong D 3rd, Nagendran MV, et al. *J Rheumatol.* 2002 Aug;29(8):1708-12.

*The preceding abstracts were obtained from Medline service maintained  
by the National Institutes of Health*