(commercially, Hymovis®) of HA on some inflammatory aspects of the osteoarthritis process reproduced in vitro.
Methods: The human leukemic monocytic cell line THP-1 was treated with CPP crystals (0.025 mg/ml) or LPS (500 ng/ml) and cultured for 24 hours with either simultaneous or 30' delayed addition of fresh media containing 0.5 mg/mL unmodified HA (HN 500-730 kDa, HX >1,500 kDa) or the hexadecylamide derivative of HA (Hymovis®) (HS), all supplied by Fidia Farmaceutici SpA. In some experiments, cells were primed for 3 h with PMA at 300 ng/ml or pre-treated for 2 h with CD44 function-blocking monoclonal antibody (10 μg/ml) or an isotype control prior to stimulation. The levels of IL-1ß and IL-8 were determined in the culture supernatants by ELISA assays. The effect of HA on the phagocytic capacity of THP-1 was evaluated by ordinary/polarized light microscopy. The scavenger effect of HA on cytokines was determined through the indirect quantification of the binding of these proteins to the chemical structure of HA. The expression of CD44 on THP-1 cells was assessed by fluorescence-activated cell sorter (FACS) analysis.
Results: THP-1 cells produce high basal levels of both IL-1ß and IL-8 which further increase after 24 h treatment with CPP crystals. The addition of 0.5 mg/mL of HA along with the stimulus lead to about the 60% inhibition of cytokine release using HS with compared to HN and HX. Any scavenger effect of HS due to the binding of IL-1ß and IL-8 to its chemical structure was ruled out. HS displayed a moderate inhibitory effect on crystal phagocytosis. All three derivatives showed a strong inhibitory effect on LPS-induced IL-1ß and IL-8 production when added simultaneously with the stimulus, but only HS was able to block inflammation once started. This effect was confirmed in presence of CPP crystals. THP-1 constitutively express CD44 receptor as evidenced by FACS analysis. Nevertheless, the incubation with the anti-CD44 antibody did not alter HS effect on THP-1 inflammatory response.
Conclusions: The results of this study show that the hexadecylamide derivative of HA is able to suppress IL-1ß and IL-8 production after CPP crystal and LPS stimulation of monocytes. The fact that 1) HS, but not unmodified HA, acts also once inflammation is triggered, 2) it do not exhibit scavenger effect and 3) its action is not stimulus-specific, allows us to hypothesize that the anti-inflammatory activity of HS could be modulated by its interaction with components/receptors of cell surface other than CD44, at least in this model.

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CIRCULATING C-REACTIVE PROTEIN IN OSTEOARTHRITIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Purpose: There is emerging evidence that the development and progression of osteoarthritis (OA) is associated with inflammation. C-reactive protein (CRP), a systemic marker for inflammation, may be elevated in OA patients but the evidence is conflicting. We systematically reviewed the literature for the relationship between serum CRP levels measured by a high sensitivity method (hs-CRP) and OA, as well as the correlation between circulating CRP levels and OA phenotypes.
Methods: MEDLINE, EMBASE and CINAHL databases were systematically searched from January 1992 to December 2012. Studies were included when they met the inclusion criteria and data from studies were extracted. Two independent reviewers assessed study quality using a modified Newcastle-Ottawa Quality Assessment Scale (NOQAS). Meta-analyses were performed to pool available data from included studies. MEDLINE, EMBASE and CINAHL databases were systematically searched from January 1992 to December 2012. Studies were included when they met the inclusion criteria and data from studies were extracted. Two independent reviewers assessed study quality using a modified Newcastle-Ottawa Quality Assessment Scale (NOQAS). Meta-analyses were performed to pool available data from included studies.
Results: Ten case-control, 15 cross-sectional, 4 longitudinal studies and 3 clinical trials met the criteria and were thus included. Data of 17,090 participants (6,440 OA cases and 10,650 controls) were extracted. The average methodological quality across included studies was satisfactory. Except for one study showing no difference between OA and controls, all other studies revealed that circulating levels of hs-CRP were higher in OA patient than in healthy controls (Fig. 1). The pooled mean difference showed that hs-CRP level was significantly higher in OA than in controls, with an average increase in value of 1.19 mg/l (95% CI 0.64 to 1.73, $p < 0.001$). The elevation in serum hs-CRP levels was greater in hip OA than in knee OA, 3.37 mg/l (95% CI 0.60 to 6.13) compared to 1.15 mg/l (95% CI 0.18 to 2.12). The links between serum hs-CRP levels and knee radiographic OA were investigated in four studies. The pooled correlation coefficient showed that the link between serum hs-CRP levels and knee radiographic OA was weak and it was not statistically significant ($r = 0.11$, 95% CI −0.03 to 0.26, $p = 0.13$). The correlation coefficients between hs-CRP levels and pain in OA patients were available in six studies. The pooled result of the meta-analysis showed that there was a weak but statistically significant correlation between hs-CRP levels and pain scale score ($r = 0.14$, 95% CI 0.08 to 0.20, $p < 0.001$). There was no significant heterogeneity observed across the studies ($Chi2 = 4.12$, $p = 0.39$; $I2 = 3\%$). Two studies reported the correlation coefficient of hs-CRP with physical function. The results from both studies were consistent with each other, indicating a correlation between increased hs-CRP levels and worsening physical function. The pooled correlation coefficient was statistically significant ($r = 0.26$, 95% CI 0.13 to 0.39, $p < 0.001$)
Conclusions: OA is chronic joint disorder with low grade systemic inflammation as reflected by increased serum hs-CRP levels. Low-grade systemic inflammation may play a greater role in symptoms rather than radiographic changes in OA.

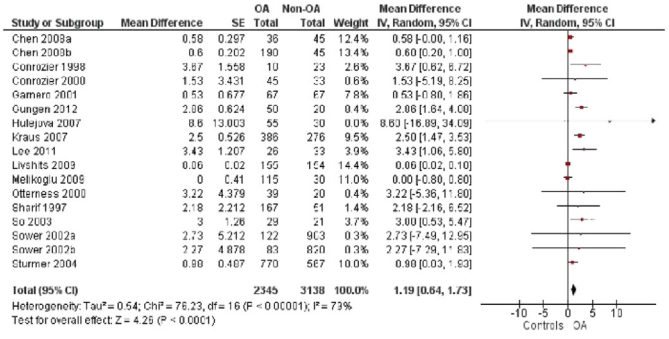

Fig. 1. Comparison of hs-CRP levels between OA and non-OA

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OLIGOMYCIN, AN INHIBITOR OF COMPLEX V OF THE MITOCHONDRIAL RESPIRATORY CHAIN, INDUCES AN INFLAMMATORY AND OXIDATIVE RESPONSE IN RAT KNEE JOINT.

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Purpose: Inflammation is now recognized as a pivotal player in articular damage pathways in OA. A decline of mitochondrial function has been described in OA chondrocytes and RA synoviocytes. Recent ex vivo findings support a connection between mitochondrial dysfunction and activation of inflammatory and destructive pathways in these cells. The aim of this study was to investigate in vivo whether the intraarticular injection of oligomycin (OLI), an inhibitor of mitochondrial function, induces a destructive, oxidative and inflammatory response in rat knee joints.
Methods: 45 female wistar rats (180–220 g) were randomized into three study groups: Healthy (no intraarticular injection); Lipopolysaccharide (LPS)-treated, positive control (left joint injected with 10 μg LPS); and OLI-treated (left joint injected with 20 μg OLI). Right joints were treated with the respective vehicles. Intraarticular injections were carried out on day 0, 2 and 5, and rats were euthanized on day 6. Hind paws were collected and joint tissues were obtained. Measurement of joint diameters on stimulis- and control-injected paws was performed on days 0 and 6. Histopathologic lesions were evaluated by Hematoxilyn-Eosin (H&E) and Masson Trichromic Staining in synovial tissue and by Safranin O staining in cartilage. ROS production was