Figure 1: Plasma level of CX3CL1 and CCL26 and expression of CX3CR1 in various subsets of PBMCs. In comparison with HCs, patients with PBC present with following features. (A) A significantly higher plasma level of CX3CL1. (B) An increased tendency of CCL26 level in plasma. (C) A significantly larger percentage of CX3CR1⁺ cells in CD4⁺ T cells. (D) A comparable expression of CX3CR1 in CD8⁺ T cells. (E) A comparable expression of CX3CR1 in NK cells. (F) A significantly larger percentage of CX3CR1⁺ cells in NKT-like cells.

Figure 2: Expression of CX3CL1 and CCL26 in liver tissues and the change of CX3CL1/CCL26-CX3CR1 pathway expression in HIBECs upon stimulation of various cytokines. (A-D) In intrahepatic bile ducts, high expression of CX3CL1 and CCL26, which was indicated by arrows and triangles respectively, was observed in PBC patients. However, only weak expression of CX3CL1 and no expression of CCL26 were found in HCs. (E-F) Weak and no expression of CX3CL1 was revealed in hepatocytes in PBC patients and HCs respectively. (G-H) CCL26 was widely expressed in both PBC patients and HCs. However, in PBC patients, hepatocytes expressed with CCL26 tended to be abundant near portal areas and became scarce in distant regions. This distribution pattern was not observed in HCs. (I) IFN- γ up-regulated the expression of CX3CL1 in HIBEC culture supernatant. (J) IL-4 and IL-13 stimulated the expression of CCL26 in HIBEC culture supernatant. (K) IFN- γ stimulated the expression of CX3CR1 on HIBEC surface.

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AB0082

REDUCED STEROIDOGENIC ACTIVITY OF REPOSITORY CORTICOTROPIN INJECTION (RCI) INDUCES A DISTINCT CYTOKINE RESPONSE FOLLOWING T CELL ACTIVATION IN VIVO

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Background: Melanocortin receptor agonists, such as α MSH have been shown to reduce inflammation in preclinical models, suppressing the production of pro-inflammatory cytokines. Natural and synthetic ACTH analogues remain linked to the induction of corticosteroids as their primary mechanism of action, leading to the anti-inflammatory and immunosuppressive responses. Repository Corticotropin Injection (RCI) is a complex mixture containing purified porcine pituitary ACTH-analogue, and is an FDA-approved treatment for several inflammatory diseases. RCI has been shown to be effective in steroid-refractory autoimmune disease.

Objectives: We hypothesize that Acthar has an immune regulatory response distinct from synthetic ACTH and steroids. These studies sought to explore the differences between RCI and synthetic ACTH on corticosterone levels in rats and cytokine production in a murine T cell activation model.

Methods: RCI (10, 40, or 400 IU/kg) or ACTH (0.6, 1.2, or 2.4 mg/kg) was administered to Sprague Dawley rats, plasma samples collected and analyzed for corticosterone. To determine the effect on T cell cytokine production, Balb/C mice were treated with RCI (10, 40, and 400 U/kg), ACTH (0.6, 1.2, or 2.4 mg/kg) or prednisolone 1 hour prior to the administration of an anti-CD3. Two hours after antibody administration, plasma cytokines were measured using Meso Scale multiplex ELISA.

Results: RCI and ACTH peak corticosterone and area under the curve (AUC) were evaluated. RCI-induced corticosterone rapidly peaked between 2-8 hrs. and was dependent on the dose. ACTH displays a delay in the peak time (8-24 hours) and was not dose dependent. When compared to the high dose ACTH, RCI reduced the AUC by 50.0 $\pm$ 2.6%, 45.5 $\pm$ 5.6% and 27.3 $\pm$ 12.5% respectively for 10, 40, and 400 IU/kg. However, there was no significant reduction between any of the ACTH doses tested.

To further explore functional differences between RCI and ACTH, we examined the effects on T cell activation. In vivo T cell activation with the anti-CD3 antibody (clone, 145-2C11) increased several cytokines, including IL-2, IL-6, IL-10, and IFN γ . Treatment with RCI, ACTH, or prednisolone significantly reduced the production of IL-2, IL-4, IFN γ , and TNF α . Interestingly, RCI showed an inverse dose-response on the production of IL-6 and IL-10. RCI inhibited the production of IL-6 at 74.7 $\pm$ 4.4% and 67.9 $\pm$ 8.5% and IL-10 at 39.1 $\pm$ 7.1% and 26.7 $\pm$ 9.3% for 10 and 40 IU/kg, respectively, whereas 400 IU/kg had no effect. ACTH inhibited the production of IL-6 at a similar level for all doses tested and had no effect on IL-10 production, whereas treatment with prednisolone inhibited all cytokines.

Conclusion: These data show that RCI has a reduced steroidal response compare to synthetic ACTH. RCI has a direct and distinct immunomodulatory response on T cells unique from both synthetic ACTH and steroids. These characteristic effects suggest a mechanism of action for RCI that is steroid-independent and may help explain its benefit in steroid refractory syndromes.

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AB0083

ADIPONECTIN STIMULATES PRO-INFLAMMATORY CYTOKINE PRODUCTION BY PERIPHERAL BLOOD MONONUCLEAR CELLS FROM PATIENTS WITH EARLY UNTREATED RHEUMATOID ARTHRITIS

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Background: The pathogenesis of rheumatoid arthritis (RA) involves the action of immune cells and fibroblast-like synoviocytes (FLS). Adiponectin, an adipokine produced mainly by adipocytes, is elevated in serum of RA patients compared to healthy controls; moreover, synovial fluid from RA subjects has higher levels of adiponectin compared to controls with osteoarthritis^{1,2}. Adiponectin induces the production of pro-inflammatory cytokines, such as interleukin 6 (IL-6) and IL-8, by

FLS from RA patients^{3,4}. However, it remains unclear whether the response to adiponectin in terms of cytokine production is different in immune blood cells from healthy donors compared to RA patients; moreover, it is not known if FLS from healthy subjects can also produce pro-inflammatory cytokines upon adiponectin stimulation.

Objectives: The study aims to analyse if adiponectin induces pro-inflammatory cytokine production by peripheral blood mononuclear cells (PBMCs) from both early RA patients and healthy controls. We also aim to study whether adiponectin induces pro-inflammatory cytokine production by FLS from healthy subjects.

Methods: PBMCs were isolated from whole blood obtained from 5 healthy donors and 3 early untreated newly diagnosed RA patients using Ficoll-Paque PLUS. FLS were isolated from synovial tissue obtained from 3 healthy donors after knee surgery due to injury. Healthy FLS were cultured in Dulbecco's Modified Eagle Medium (DMEM GlutaMAX) supplemented with 10% FBS, 1% Penicillin-streptomycin and 0.5% Gentamycin. Harvested PBMCs and FLS were resuspended in X-VIVO 15 serum-free hematopoietic cell medium and stimulated with different doses of human recombinant adiponectin (1, 5 and 10 µg/ml), and the culture media were collected at different time points. Concentrations of IL-6, IL-8 and TNF-α were measured with ELISA.

Results: Unstimulated PBMCs from early RA patients produced higher levels of IL-6 compared to healthy subjects ($P < 0.001$). In healthy controls, both the production of IL-6 and TNF-α was higher in PBMCs stimulated with adiponectin compared to unstimulated PBMCs ($n=5$, $P < 0.01$ for IL-6 and $P < 0.01$ for TNF-α). Likewise, the production of both IL-6 and TNF-α was higher in PBMCs from early-RA patients after stimulation with adiponectin compared with unstimulated PBMCs ($n=3$, $P < 0.01$ for IL-6 and $P=0.03$ for TNF-α) in a dose- and time-dependent manner. After stimulation with adiponectin, levels of IL-6, but not TNF-α, were higher in PBMCs from subjects with early RA compared to healthy controls ($P < 0.01$). Adiponectin stimulation did not induce IL-8 production from PBMCs from either healthy donors or RA patients.

Adiponectin was able to induce the production of IL-6 and IL-8 by FLS isolated from healthy donors ($n=3$, $P=0.03$ for IL-6 and $P=0.02$ for IL-8), but not TNF-α.

Conclusion: Our results show that adiponectin induces the production of IL-6 and TNF-α from PBMCs from both healthy subjects and patients with RA and that adiponectin is able to stimulate the production of IL-6 and IL-8 by FLS isolated from healthy subjects. Those results suggest that adiponectin may play a role in the pathogenesis of RA.

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Cartilage, synovium and bone

AB0084

ASSOCIATION OF SYNOVITIS VERSUS CARTILAGE LOSS WITH PAIN SEVERITY AND FUNCTIONAL LIMITATION IN PRIMARY KNEE OSTEOARTHRITIS: CLINICAL, ULTRASONOGRAPHY AND MAGNETIC RESONANCE IMAGING

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Background: Osteoarthritis (OA) is a common and debilitating condition associated with pain and the loss of mobility that undermines quality-of-life. Magnetic resonance imaging (MRI) has become the most important modality for assessment of pathologic changes in knee cartilage, in both clinical and research environment, also Musculoskeletal Ultrasound (MSU) is a valuable tool for imaging musculoskeletal changes in osteoarthritis. It shows early and late changes.

Objectives: The aim of the study was to detect the association of MRI and musculoskeletal ultrasound detected synovitis versus cartilage defect with knee pain severity and functional limitation in patient with primary knee osteoarthritis

Methods: This study was carried out on fifty patients of primary osteoarthritis diagnosed as primary osteoarthritis of knee joints according to American College of Rheumatology Radiologic and Clinical Criteria for Knee osteoarthritis all patients were assessed clinically and knee examined for any swelling tenderness, warmth, limitation of range of motion. Pain severity and functional limitation assessed by Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Musculoskeletal ultrasound and M.R.I of osteoarthritic knee joints were done.

Results: MSUS synovitis of examined joints was (0.93 ± 0.94) and cartilage thickness (3.95 ± 1.4). MRI synovitis of examined joints was (0.89 ± 0.93) and cartilage thickness (39.9 ± 13.26). There was Correlation between WOMAC pain score and MSU synovitis and cartilage thickness with Significant difference ($p < 0.01$), also there was Correlation between WOMAC pain score and MRI synovitis and cartilage thickness with Significant difference ($p < 0.01$). a positive Correlation between MSU Synovitis and MSU cartilage thickness was detected Significant difference ($p < 0.01$) $r(0.38)$. Also a Correlation between MRI Synovitis and MRI cartilage thickness show Significant difference ($p < 0.01$) $r(0.39)$.

Sagittal an proton density-weighted magnetic resonance imaging shows focal cartilage loss in the lateral tibiofemoral joint

Conclusion: The severity of cartilage loss and severity of the synovitis/effusion are the most significant determinants of pain and functional disability. Synovitis has role on increasing cartilage loss MRI and MSU are a non-invasive method which allows comprehensive assessment and detection of early structural changes in osteoarthritic joints

Longitudinal scan show first grade of synovitis of right knee

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AB0085

ULTRASONOGRAPHIC EVALUATION OF THE METACARPAL CARTILAGE THICKNESS IN WEIGHTLIFTERS AND VOLLEYBALL PLAYERS

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Background: Articular cartilage is inevitably exposed to impact and loading in different sports play. Despite the fact that it is quite prone to different forms of overloading, the metacarpal cartilage has not been looked into in the pertinent literature. Accordingly, in this comparative study, we have assessed the metacarpal cartilage in volleyball players and weightlifters whereby different forms of stress is naturally prevalent in the athletes' hands.