CCP levels. No patients had IgA anti-CCP detectable in both saliva and sputum samples.

Abstract OP0270 – Table 1

	Anti-CCP positive results (%)					
	Saliva IgA	Sputum IgA	Serum IgA	Saliva IgG	Sputum IgG	Serum IgG
HC	1/31 ⁽¹⁾	1/22 ⁽¹⁾	1/32 ⁽¹⁾	1/31 ⁽¹⁾	0/22 (0)	0/32 (0)
CCP+at-risk	8/55 ⁽¹³⁾	1/24 ⁽¹⁾	23/54 ⁽¹³⁾	23/54 ⁽¹³⁾	10/24 ⁽¹²⁾	50/54(93)
RA	10/40 ⁽¹⁵⁾	1/14 ⁽¹⁾	21/48 ⁽¹⁴⁾	23/42(55)	9/14(64)	47/48(98)

Conclusions: We found an increased prevalence of saliva but not sputum IgA anti-CCP antibodies in seropositive at-risk individuals. These findings support the concept that localised RA-related autoimmunity in at risk individuals can be site specific. IgA anti-CCP antibodies at the oral mucosa precede arthritis and may represent an important step in the initiation and propagation of disease.

REFERENCES:

- [1] Brandtzaeg P. *Ann NY Acad Sci* 2007.
- [2] Willis, et al. *Arthritis Rheum* 2013.

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OP0271

GASTROINTESTINAL DAMAGE AND MICROBIAL TRANSLOCATION ARE INVOLVED IN THE DEVELOPMENT OF IMMUNE SYSTEM ACTIVATION IN INFLAMMATORY BOWEL DISEASE-ASSOCIATED SPONDYLOARTHRITIS

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Background: The altered composition of the gastrointestinal (GI) microbiota, known as dysbiosis, can induce and modulate the systemic inflammation, through microbial translocation and T-cell activation, in several immuno-mediated diseases, such as inflammatory bowel disease (IBD), HIV infection, and ankylosing spondylitis.

Objectives: In a cohort of 85 patients with inflammatory bowel disease-associated spondyloarthritis (SpA/IBD), we assessed gut bacterial infiltration and intestinal damage. In systemic circulation, GI epithelial damage, microbial translocation and immune system activation were assessed with intestinal-fatty acid binding protein (I-FABP), lipopolysaccharide (LPS), soluble CD14 (sCD14), respectively. Moreover, the *in vitro* activity of the latter two was evaluated on osteoblast cells.

Methods: I-FABP, LPS, sCD14, sclerostin (SOST) and anti-SOST antibodies (anti-SOST-IgG) were assayed with ELISAs. LPS and sCD14 were used *in vitro* to stimulate the MG63 human osteoblast-like cell line. Occludin, claudin-1, claudin-4, and the presence of bacteria were assessed, respectively, by real-time-PCR analysis and immunohistochemical staining of the ileum.

Results: Bacteria were detectable in the ileal epithelium of IBD patients, but only in SpA/IBD they were associated with epithelial damage and downregulation of occludin, claudin-1 and claudin-4 (figure 1A-B).

The serum levels of I-FABP, LPS and sCD14 resulted significantly higher in axial (187.9, 14.03, and 26.97, respectively) and peripheral SpA/IBD (130.3, 11.55, and 18, respectively) than in IBD patients (IFABP 43.65, $p<0.0001$ for both patients' groups; LPS 9.625, $p<0.0001$ vs Ax-SpA/IBD and $p=0.007$ vs Per-SpA/IBD; sCD14 12.34, $p<0.0001$ for both patients' groups) (figure 1C).

In the SpA/IBD cohort, SOST was weakly correlated with I-FABP ($r=0.2683$), LPS ($r=0.3063$) and sCD14 ($r=0.3075$), and anti-SOST-IgG with LPS ($r=0.3959$) and sCD14 ($r=0.3414$). Moreover, sCD14 showed significant correlation with I-FABP ($r=0.3316$) and LPS ($r=0.5649$).

In vitro, LPS, but not sCD14, significantly induced SOST expression through the upregulation of both Wnt3a and Wnt5a and the downregulation of the b-catenin proteins (figure 1D). On the opposite, the combination of LPS and sCD14 downregulated SOST expression through the upregulation of ERK1/2 and b-catenin protein (figure 1D).

Abstract OP0271 – Figure 1 A. immunohistochemical staining of ileal bacteria. Ten ileal samples of patients affected by SpA/IBD or IBD were stained for bacteria infiltration (upper panel). Lower (from left to right): Gram and LPS staining of the same samples. B. Analysis of ileal tight-junctions proteins expression. From the left to the right: Ten ileal samples of patients affected by SpA/IBD or IBD were stained for occludin (and claudin-1 and -4, data not shown); count of occludin positive cells and quantitative real-time-PCR of occludin (and claudin-1 and -4, data not shown) expression in the same ileal samples. C. analysis of I-FABP, LPS and sCD14 serum levels in SpA/IBD and IBD patients. ELISAs assays were carried out in 45 patients with axial and 40 patients with peripheral SpA/IBD, and compared with IBD or HC. D. Western-blot analysis of MG-63 osteoblast-cells. The MG-63 osteoblast-like cell line was stimulated with LPS $\pm$ sCD14 *in vitro* and then cells were harvested for western blot analysis. Semi-quantitative densitometric analysis of the protein bands was carried out on the blot (data not shown). Statistical analysis: Kruskal-Wallis analysis. ** $p<0.01$; **** $p<0.0001$; if not reported: p not significant. Abbreviations. SpA/IBD: inflammatory bowel disease-associated spondyloarthritis; ax-SpA/IBD: axial SpA/IBD; peripheral SpA/IBD; IBD: inflammatory bowel disease; HC: healthy controls; I-FABP: intestinal fatty acid binding protein; LPS: bacterial lipopolysaccharide; sCD14: soluble CD14; ERK 1/2: extracellular Signal-regulated Kinase-1/2. Wnt: wingless protein family; SOST: sclerostin.

Conclusions: The role of gut inflammation and microbial translocation in the onset of arthritis in IBD patients are still under investigation. We have demonstrated that in SpA/IBD there is a significant bacterial infiltration of the ileal tract, associated with the downregulation of tight-junctions' proteins (occludin, claudin-1 and claudin-4) and epithelial damage, that cause microbial translocation and higher plasma levels of I-FABP, LPS, and sCD14. LPS and sCD14, thus, could trigger a complex systemic inflammatory response acting on several biochemical pathways, linking the immune system (anti-SOST-IgG) and the bone (SOST).

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OP0272

INFLAMMATION AT BARRIER TISSUES SUCH AS SKIN AND GUT TRIGGERS MILD JOINT INFLAMMATION AND IS INFLUENCED BY BIOMECHANICAL STRESS INDUCED BY FORCED-RUNNING

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Background: The factors triggering the onset of psoriatic arthritis (PsA) and other forms of spondyloarthritis (SpA) are mostly unknown. These joint diseases are clinically associated with psoriasis (PsO) and inflammatory bowel disease (IBD). The three pathologies share the common leitmotiv of chronic inflammation and all of them have an at least partially shared genetic susceptibility. Entheses, the attachment sites of tendons and ligaments into the bones, are considered as a primary disease localization and a site of biomechanical stress. Increasing evidence supports the hypothesis that biomechanical stress, together with inflammatory triggers such as antigens and changes in the microbiome, can contribute to the onset of PsA and SpA by inducing local microdamage in the entheses.

Objectives: Here, we aim to understand early events leading to PsA and SpA by combining a protocol of forced exercise in mice with simultaneous locally-induced cutaneous or intestinal inflammation.

Methods: Forty 8 weeks old C57/Bl6 male mice were used to induce the PsO- or IBD-like disease, respectively by serial applications of imiquimod cream (IMQ) on a shaved area of the back skin, and administration to the intestine of dextran sodium sulphate (DSS) dissolved in drinking water. Forty control mice were left

untreated. After induction of inflammation, we applied a protocol of forced treadmill running to increase biomechanical stress in half of the mice. Control mice with or without IMQ or DSS treatment did not run. We evaluated skin and gut disease severity clinically and by histology, and performed microCT scans, histological and immunohistochemical analyses of the knees and the paws, to investigate eventual changes occurring in the joints.

Results: Clinical and histological assessment of the skin or gut confirmed successful induction of cutaneous and intestinal inflammation. The exercise protocol slightly affected the severity of the PsO- but not of the IBD-like disease in mice. In both models, disease was not confined to the target organs as systemic inflammation was demonstrated by trabecular bone loss, as indicated by microCT analyses, and by changes in spleen size. The exercise protocol did not appear to have an additional effect on these systemic disease manifestations, but it is associated with increased articular cartilage thickness and cellularity. Signs of mild joint inflammation were seen for both the IMQ and DSS models. Mild synovitis was triggered by skin and gut disease. At the entheseal level, immunohistochemical detection for CD45⁺ cells showed that forced exercise boosts inflammation in the presence of inflammation triggered at a distant site.

Conclusions: Induction of PsO- or IBD-like inflammation by local treatments of immune-privileged barrier tissues, such as skin and gut, also triggers a systemic response with inflammation-associated bone loss and discrete signs of joint disease. Forced running exercise increased the degree of enthesitis in this setting, providing new support for the hypothesis that biomechanical stress contributes to disease manifestations in PsA and other forms of spondyloarthritis.

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OP0273 TRANSMEMBRANE TNF SIGNALLING THROUGH TNF-RI INDUCES SPA-LIKE INFLAMMATION, WHEREAS SIGNALLING THROUGH TNF-RII IS CRUCIAL FOR NEW BONE FORMATION

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Background: TNF can drive strictly distinct inflammatory pathologies depending on its expression form. Previously, we have shown that transmembrane (tm) TNF rather than soluble TNF contributes to key pathological features of spondyloarthritis (SpA), including new bone formation.¹

Objectives: Delineate the cellular and molecular mechanisms by which selective tmTNF overexpression leads to SpA-like pathology.

Methods: tmTNF tg mice (TgA86)² were crossed with TNF-RI or TNF-RII knock out mice. Animals were followed for 100 days for clinical symptoms of arthritis and spondylitis development. Histology was performed at the end of the study on both peripheral and axial joints. Calvarial mouse fibroblasts were cultured in osteogenic conditions. Differentiation towards osteoblasts was analysed by alizarin red staining, alkaline phosphatase (ALP) staining as well as by qPCR for collagen type I, II, and X, ALP and RUNX2.

Results: Clinical arthritis, visualised by swelling and deformation of front- and hind paws, was observed in 100% of the tmTNF^{+/WT} (>20) as well as in all tmTNF^{+/WT}xTNF-RII^{-/-} mice (7/7) but not in tmTNF^{+/WT}xTNF-RI^{-/-} mice (0/9). Histologically, peripheral synovitis, osteitis and enthesitis were observed in all tmTNF^{+/WT} and tmTNF^{+/WT}xTNF-RII^{-/-} mice, confirming previous findings that tmTNF-mediated synovitis requires the presence of the TNF-RI receptor.² Similarly, hunch back formation and crinkled tails were observed in the tmTNF^{+/WT} and the tmTNF^{+/WT}xTNF-RII^{-/-} mice but not in tmTNF^{+/WT}xTNF-RI^{-/-} mice. Histology confirmed the presence of inflammatory cellular infiltrates at the edge of the intervertebral units in all tmTNF^{+/WT} tg mice and all tmTNF^{+/WT}xTNF-RII^{-/-} mice, but not in tmTNF^{+/WT}xTNF-RI^{-/-} mice. Whereas these data indicate that TNF-RI is required for tmTNF-induced inflammation, it was striking that 50% (10/20) of the tmTNF^{+/WT} versus none (0/7) of the tmTNF^{+/WT}xTNF-RII^{-/-} mice depicted clear histological signs of endochondral new bone formation. To test whether TNF-RI is involved in pathological new bone formation in this model, calvarial fibroblasts skulls from tmTNF^{+/WT}, tmTNF^{+/WT}xTNF-RI^{-/-}, tmTNF^{+/WT}xTNF-RII^{-/-} or WT were differentiated with osteogenic medium with or without IL-17A. tmTNF overexpressing fibroblasts enhanced the osteogenic differentiation as observed by ALP and alizarin red staining and increased mRNA levels of Collagen type I and ALP compared to WT. This enhancement in osteogenesis was maintained in tmTNF^{+/WT}xTNF-RI^{-/-}-derived fibroblasts but abolished in tmTNF^{+/WT}xTNF-RII^{-/-}-derived fibroblasts.

Conclusions: The SpA-like phenotype in tmTNF tg mice is crucially dependent on TNF-RI to drive peripheral and axial inflammation, but TNF-RII signalling is required to drive the pathological new bone formation under inflammatory conditions.

REFERENCES:

- [1] Van Duivenvoorde L, van Tok M, Baeten D. *Annals of the Rheumatic Diseases* 2014;73:441–441.
- [2] Alexopoulou L, Pasparakis M, Kollias G. *Eur J Immunol* 1997;27(10):2588–92.

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HPR Supporting self-management

OP0274-HPR A FUNCTIONAL EXERCISE PROGRAM IMPROVES PAIN AND HEALTH RELATED QUALITY OF LIFE IN PATIENTS WITH FIBROMYALGIA: A RANDOMISED CONTROLLED TRIAL

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Background: Fibromyalgia (FM) is a syndrome characterised mainly by chronic generalised pain that affects the physical fitness and functional capacity of patients. There is increasing evidence of the benefits of physical exercise in improving FM symptoms, making these interventions part of therapeutic arsenal.

Objectives: To evaluate the effectiveness of a program of functional exercises in reducing pain, improving functional capacity, increasing muscle strength, improving flexibility, balance and quality of life of patients with FM.

Methods: It is a controlled and randomised study, with blind evaluator. A total of 82 female patients with FM were included, with age between 18 and 65 years, randomised into two groups, intervention and control. The intervention group (FEG) performed functional exercise training for 45 min twice a week for 14 weeks. The control group (SEG) performed stretching exercises with the same duration and frequency. Evaluation instruments were: VAS – Visual Analogue Scale for pain assessment; FIQ- Fibromyalgia Impact Questionnaire, for assessing health-related quality of life; Time-up and go test for functional performance evaluation; 1 RM, for evaluation of muscle strength; Bank of Welss, for the assessment of flexibility; Berg Balance Scale, to evaluate balance; and SF-36 to evaluate general quality of life. Also, the amount of analgesics used during the intervention period was assessed.

Results: 41 patients were randomised to the FEG and 41 patients to the SEG. After intervention, the FEG presented a reduction in pain and an improvement in the quality of life related to the disease, which was statistically significant compared to SEG. Regarding general quality of life, functional capacity, muscle strength, flexibility and balance, there was no difference between the groups.

Conclusions: Functional exercise training proved to be effective in reducing pain and improving the health-related quality of life of patients with FM when compared to stretching exercises.

REFERENCES:

- [1] Wolfe F, Clauw D, Fitzcharles MA, Goldenberg D, Katz RS, Mease P, et al. The American College of Rheumatology Preliminary Diagnostic Criteria for Fibromyalgia and Measurement of Symptom Severity. *Arthritis Care Res* 2010;62:600–10.
- [2] Hauser W, Klose P, Langhorst J, et al. Efficacy of different types of aerobic exercise in fibromyalgia syndrome: A systematic review and meta-analysis of randomised controlled trials. *Arthritis Res Ther* 2010;12:R79.
- [3] Burchardt CS. Multidisciplinary approaches for management of fibromyalgia. *Curr Pharm Des* 2006;12:59–66.

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