has been associated with IL-17A-mediated inflammatory diseases, including PsA and AS.^{3,4} IL-17F production in MAIT cells remains largely unexplored.

Objectives: To explore the importance of IL-23 signalling in MAIT cell-derived IL-17A and IL-17F production, examine the presence of MAIT cells in psoriatic lesional skin and assess the contribution of MAIT cell-derived IL-17A and IL-17F using *in vitro* models of skin inflammation.

Methods: IL-17A and IL-17F production by MAIT cells was assessed by flow cytometry, ELISA, qPCR and CyTOF upon activation by anti-CD3/CD28 or fixed *E. coli* via MR1-presented riboflavin metabolites, with or without disease-relevant recombinant cytokines or an IL-23-neutralising antibody. RNAscope was utilised to observe MAIT cells in psoriatic lesional skin. MAIT cell supernatant, generated from FACS sorted activated MAIT cells, was cultured with normal human dermal fibroblasts (NHDFs) in the presence of IL-17-isoform-specific antibodies, including bimekizumab, a monoclonal antibody that potently and selectively neutralises both IL-17A and IL-17F.

Results: Optimal MAIT cell IL-17A and IL-17F production occurred upon T cell receptor triggering with IL-12 and IL-18, independently of IL-23. IL-17F expression was greater at both gene and protein levels than IL-17A. The kinetics and threshold of activation for IL-17A and IL-17F suggest tighter regulation compared with other inflammatory cytokines, including IFN γ and TNF. Optimal MAIT cell IL-17A and IL-17F production requires monocytes, which contribute to IL-12 production upon IL-18 stimulation. MAIT cells were abundant in psoriatic lesional skin. NHDFs cultured with supernatant generated from activated MAIT cells produced inflammatory mediators IL-6, IL-8 and CCL2, which were reduced upon inhibition of either IL-17A or IL-17F, with optimal suppression achieved following dual neutralisation with bimekizumab.

Conclusion: IL-17A and IL-17F can be produced from MAIT cells independently of IL-23, and contribute to inflammatory responses in NHDFs. These results support dual neutralisation of IL-17A and IL-17F as a complete and targeted approach to suppress IL-17-driven inflammatory responses.

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OP0303

MONOSODIUM URATE AND CALCIUM PYROPHOSPHATE CRYSTAL-INDUCED INTERLEUKIN 1 PRODUCTION DEPENDS ON GLUCOSE UPTAKE THROUGH GLUT1 TRANSPORTER

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Background: Monosodium urate (MSU) and monocalcium pyrophosphate dihydrate (mCPPD) crystals are responsible for relapsing acute arthritis which is driven by interleukin 1 β (IL-1 β). IL-1 β production relies on NLRP3 inflammasome activation leading to ASC and caspase-1 recruitment. In tumor cells and in LPS-stimulated macrophages a switch of cell metabolisms toward glycolysis favors IL-1 β production.

Objectives: The aims of this study were to assess 1/whether crystal-induced NLRP3 activation and IL-1 β production involved glucose metabolism and 2/how MSU and mCPPD crystals induced glucose uptake focusing on the role of glucose transporter Glut1.

Methods: Synthetic and pyrogen-free MSU and mCPPD crystals were used to stimulate THP-1 cells and mouse bone marrow-derived macrophages (BMDM). Cells were stimulated in presence or absence of glucose (2g/L) and pyruvate (10mM). Glycolysis was inhibited by 2-deoxy-glucose (2DG) and the role of

glucose transporter 1 (Glut1) was assessed by pharmacological inhibitor (STF-31) and siRNA. IL-1 β production was quantified by ELISA. Metabolomic analysis was performed by mass spectrometry. Glucose uptake was determined using ¹⁸F-DG (Fluor18 labeled-2DG) and positron emission tomography (PET). Glut1 membrane localization was assessed by flux cytometry and confocal microscopy. ASC speck formation by confocal microscopy. *In vivo*, we used murine air pouch model to assess the effects of 2DG and Glut1 inhibition in crystal-mediated inflammation. Glut1 membrane localization of circulating neutrophils was compared to synovial fluid neutrophils harvested during gout flare.

Results: *In vitro*, both MSU and mCPPD crystal-induced IL-1 β secretion and ASC speck formation were inhibited when cells were cultured in glucose-free medium or in presence of 2DG. Similarly, MSU and mCPPD crystal-induced inflammation was abrogated in mice treated with 2DG. In THP-1 cells stimulated by MSU and mCPPD crystals, metabolomic analysis displayed alteration of glycolysis pathway and Krebs cycle and decrease of intracellular ATP production. Interestingly, MSU and mCPPD crystals increased glucose uptake *in vitro*, *ex vivo* and *in vivo*. Crystal-induced IL-1 β secretion was decreased by STF-31 and in THP-1 cells transfected with Glut1 siRNA. Next, we observed that MSU and mCPPD crystals increased membrane localization of Glut1 in THP-1, BMDM and neutrophils infiltrated in air pouch lavages and membranes. Glut1 membrane localization was positively correlated with IL-1 β production. Moreover, during gout flare, the proportion of Glut1 positive neutrophils was higher in synovial fluid neutrophils than in circulating neutrophils. Finally, STF-31 treatment decreased, *in vitro*, glucose uptake induced by MSU and mCPPD crystals, and *in vivo* MSU and mCPPD crystal-induced inflammation.

Conclusion: Glucose uptake through Glut1 transporter enhanced IL-1 β production induced by MSU and mCPPD crystals. Studies to decipher how these crystals induced Glut1 membrane localization are ongoing. Similarly, we investigate how glycolysis regulates NLRP3 and ASC activation. Decreasing Glut1 membrane localization might be a potential target to dampen crystal-induced inflammation.

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OP0304

GENETIC AND FUNCTIONAL STUDY OF OMENTIN REGARDING CARDIOVASCULAR RISK IN AXIAL SPONDYLOARTHRITIS

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Background: Cardiovascular (CV) disease is one of the main causes of mortality in axial spondyloarthritis (axSpA). The higher incidence of CV risk factors and systemic chronic inflammation increase CV risk in axSpA.¹ This is enhanced by a dysregulation of adipokines. Low levels of omentin, an anti-inflammatory adipokine, have been associated with metabolic dysfunction and CV disease in general population and conditions different from axSpA.^{2,3}

Objectives: To evaluate the implication of omentin in CV risk and subclinical atherosclerosis in axSpA at the genetic and functional (mRNA and protein) level.

Methods: 382 patients fulfilling the ASAS classification criteria for axSpA⁴ and 84 controls were included. Carotid ultrasound was performed to evaluate the presence of subclinical atherosclerosis. Serum omentin levels were assessed by ELISA. mRNA expression of *ITLN1*, coding omentin, was evaluated by RT-qPCR. *ITLN1* rs12409609 (C/T), in complete linkage disequilibrium with a polymorphism

previously associated with coronary artery disease,⁵ was genotyped by TaqMan probes. Results were adjusted by potential confounding factors (STATA® v.11.1). **Results:** Serum and mRNA levels of omentin were lower in axSpA compared to controls ($p<0.001$). Low omentin serum levels were observed in obese patients, patients with inflammatory bowel disease (IBD) and in those with an atherogenic index indicative of dyslipidemia ($p=0.002$, 0.006 and 0.004 , respectively). Interestingly, the C allele of rs12409609 (both when alleles and genotypes were assessed) was associated with low mRNA levels of omentin in axSpA ($p<0.001$). No association was observed between omentin and markers of subclinical atherosclerosis at the DNA, mRNA and protein level.

Conclusion: style="font-family: 'Times New Roman','serif'; font-size: 10.0pt; margin: 0cm; margin-bottom: 8.0pt; line-height: 106%; margin-left: 0cm; margin-right: 0cm; margin-top: 0cm; mso-style-name: Normal_0; text-align: justify;" font-size="11.0" data-pos-index="15" class-name="Deleted">Omentin is linked to obesity and adverse lipid profiles in axSpA. Additionally, low serum levels of omentin are associated with the presence of IBD in axSpA. These data support a role of omentin as a CV risk biomarker in axSpA.

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OP0305

THE ALARMIN S100A9 HAMPERS OSTEOCLAST DIFFERENTIATION FROM CIRCULATING PRECURSORS BY REDUCING THE EXPRESSION OF RANK

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Background: High levels of the damage-associated molecular pattern (DAMP) S100A8/A9 are produced in the inflamed synovium during experimental and human rheumatoid arthritis (RA), which have been implicated in sterile inflammation-induced bone resorption. We and others have previously shown that stimulation of mature osteoclasts with S100A8/A9 increases their bone-resorptive capacity. In agreement, reduced bone destruction was observed after induction of experimental RA models in S100a9-/- mice. However, its effects on the differentiation of osteoclasts from their precursors remains elusive.

Objectives: Here, we investigated the effects of S100A9 on osteoclast differentiation from CD14⁺ circulating precursors.

Methods: CD14⁺ monocytes were isolated from buffy coats of healthy donors and differentiated towards osteoclasts with macrophage colony-stimulating factor (M-CSF) and receptor activator of nuclear factor kappa-B (RANK) ligand in the presence or absence of S100A9. Differentiation state of osteoclasts was determined by tartrate-resistant acid phosphatase (TRAP) staining and resorption

capacity was quantified using hydroxyapatite-like-coated plates. RNA expression was analyzed with RNA sequencing and qPCR. RANK expression was assessed using FACS. Underlying epigenetic programming was studied using chromatin immunoprecipitation. Secretion of pro-/anti-inflammatory mediators was analyzed with Luminex analysis.

Results: S100A9 stimulation during monocyte-to-osteoclast differentiation resulted in a strong decrease in the numbers of multinucleated osteoclasts, underlined by a decreased resorptive capacity. The thus differentiated cells showed a high production of pro-inflammatory factors, such as interleukin (IL)-1 β , IL-6, IL-8, and tumor necrosis factor- α (TNF α) after 16h of stimulation. In contrast, at day 4, the cells showed a decreased expression of the osteoclast-promoting factor TNF α . Interestingly, we showed that S100A9 stimulation only during the first 16h of culture was sufficient to reduce osteoclastogenesis. To determine the mechanism of how this short S100A9 stimulation might reduce the osteoclast differentiation, we determined the protein expression of RANK. We observed that within this 16h time frame, S100A9 inhibited the M-CSF-mediated induction of RANK, which we found to be associated with changes in various histone marks at the epigenetic level. This S100A9-induced reduction in RANK could be partially reversed by blocking TNF α using etanercept, but not by blocking interleukin-1 (IL-1) with the IL-1 receptor antagonist.

Conclusion: Whereas S100A8/A9 was previously shown to stimulate the resorptive capacity of mature osteoclasts, we here show that early S100A9 stimulation impedes monocyte-to-osteoclast differentiation via reduction of RANK expression that is partially TNF α -mediated. This suggests that the timing of exposure to S100A8/A9 is an important determinant for monocyte-to-osteoclast differentiation.

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Public health, health services research, and health economics

OP0306

GEOGRAPHICAL VARIATION IN PATIENT OUTCOMES OF PRIMARY KNEE REPLACEMENT ACROSS CLINICAL COMMISSIONING GROUPS: STUDY FROM "THE NATIONAL JOINT REGISTRY OF ENGLAND, WALES, NORTHERN IRELAND AND THE ISLE OF MAN"

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Background: In the UK, the Health and Social Care Act 2012, places duties on the NHS Commissioning Board and Clinical Commissioning Groups (CCG) to have regard to the need to reduce variations in access to, and outcomes from, health care services for patients¹. There are well known geographical variations in the uptake of common surgical procedures including knee replacement². Much less is known about variations in outcomes of surgery and factors that can explain why such variation exists.

Objectives: Our aim was to explore variation in patients' outcomes for primary total or unicompartmental knee replacement (TKR/UKR) surgery across CCGs, and to identify whether patient, surgical and hospital factors can explain why such variation exists.

Methods: We used the National Joint Registry, which incorporates data on knee replacement surgeries. Primary operations were linked with Hospital Episode Statistics data which contains records of all inpatient episodes undertaken in NHS hospitals, and Patient Reported Outcome Measures (PROMs). Primary TKR/UKR in people aged 18 years or over between 2014 and 2016 were identified. Multilevel regression models were generated for the following outcomes: length of stay (LOS), bed costs, change in Oxford knee score (OKS) 6-months after surgery, and complication by 6 months. Models included a wide range of patient, surgical