Results: In primary synovial fibroblasts, IL37 overexpression significantly reduced IL1 β - and OAS-CM-induced expression of MMP1, MMP3, IL1B and IL6 by more than 50%. In naïve knee joints, IL-37 overexpression did not induce synovial thickening, cartilage damage or osteophyte formation and no overt immune response was detected after 28 days. Strikingly, in CIOA, at day 7, IL37 overexpression significantly reduced synovial thickening and the presence of the metalloproteinase-generated aggrecan-degradation neopeptide VDIPEN in cartilage. At day 28 of CIOA, cartilage degradation was significantly reduced by IL37 treatment at the lateral and medial femur by respectively 46% and 41%, and osteophyte size at the medial femur was reduced by 70%. At day 42 of CIOA, IL37 overexpression could no longer be detected. Osteophyte size formation at the medial femur was still significantly reduced by 46% at this time point, but only a trend ($p = 0.06$) towards reduced cartilage damage was observed on both femur and tibia.

Conclusion: Our results show that IL37 inhibits the production of catabolic mediators in synovial fibroblasts, similar to our previously obtained results in cartilage. Furthermore, IL37 clearly lowered synovial thickening and ameliorated cartilage damage and osteophyte formation in murine experimental OA. These results indicate that IL37 acts on multiple tissues and OA-related processes, which supports IL37 as a potential therapeutic agent for OA.

Disclosure of Interests: : None declared

DOI: 10.1136/annrheumdis-2019-eular.7483

FRI0527

HIGH LDL LEVELS LESSEN BONE DESTRUCTION DURING ANTIGEN-INDUCED ARTHRITIS BY INHIBITING OSTEOCLAST FORMATION AND FUNCTION

Giuliana Ascone¹, Irene DI Ceglie¹, Ilze Bot², Fons van de Loo¹, Marije Koenders¹, Peter van der Kraan¹, Arjen Blom¹, Martijn van den Bosch¹, Peter van Lent¹.

¹Radboud university medical center, Nijmegen, Netherlands; ²Leiden University, Leiden, Netherlands

Background: Rheumatoid arthritis (RA) is a chronic inflammatory disease with severe joint inflammation and bone destruction resulting from increased numbers and activity of osteoclasts as important hallmarks. RA is often associated with the metabolic syndrome, characterized by elevated levels of low-density lipoprotein (LDL), which in inflammatory environments is oxidized into oxLDL. However, the effects of high (ox)LDL levels on osteoclasts remains elusive.

Objectives: Here, we investigated the effects of high LDL and oxLDL levels on osteoclast differentiation and bone destruction.

Methods: Antigen-induced arthritis (AIA) was induced in *Apoe*^{-/-} mice that spontaneously develop high LDL levels. Bone erosion was assessed with histology and numbers of osteoclasts were determined with staining for tartrate-resistant acid phosphatase (TRAP). Numbers of CD11b⁺/Ly6C^{high} and CD11b⁺/Ly6C^{high} osteoclast precursors were determined by flow cytometry. *In vitro* osteoclast differentiation from bone marrow cells was induced with macrophage colony-stimulating factor (M-CSF) and receptor activator of nuclear factor kappa-B (RANK) for 7 days. Pre-osteoclasts from day 3 and mature osteoclasts from day 6 of differentiation were exposed to LDL/oxLDL. Gene expression was determined with qPCR.

Results: Whereas basal levels of bone resorption were comparable between WT and *Apoe*^{-/-} mice, induction of AIA resulted in significantly lower bone resorption in *Apoe*^{-/-} mice as compared to WT mice, which was associated with lower number of TRAP⁺ osteoclasts along the bone surface. However, the absence of *Apoe* did not result in altered numbers of osteoclast precursors in the bone marrow of naïve mice, whereas even increased numbers were observed in *Apoe*^{-/-} mice during AIA. Moreover, *in vitro* osteoclastogenesis showed comparable numbers and mRNA expression of osteoclast markers, such as c-Fms, RANK, NFATc1, DC-STAMP, TRAP, CTR, CIC-7, CA-II, Cat K and MMP-9. Together, this showed that the absence of *Apoe* by itself does not affect osteoclastogenesis. Therefore, we determined whether high levels of LDL cholesterol, a characteristic of *Apoe*^{-/-} mice, or oxLDL as the result of LDL oxidation by inflammation led to decreased osteoclast differentiation. Addition of oxLDL, but not LDL, to pre-osteoclasts from day 3 and mature osteoclasts from day 6 of osteoclastogenesis strongly reduced the number of TRAP⁺ osteoclasts and their resorptive capacity. This was accompanied by a decreased expression of various osteoclast markers. To determine the mechanism of how oxLDL stimulation might reduce the osteoclast differentiation, we determined the expression of RANK and various members of the co-stimulatory pathway that promotes osteoclast formation. Interestingly, whereas RANK expression was not affected upon oxLDL exposure, we observed decreased expression of osteoclast-associated receptor (*Oscar*) and the DNAX adaptor protein-12 encoding gene *Tyrbp*, which

regulate the immunoreceptor tyrosine-based activation motif (ITAM) mediated co-stimulation signaling pathway.

Conclusion: *Apoe*^{-/-} mice have decreased bone resorption during experimental RA, probably via oxLDL-mediated interference in the co-stimulatory pathway during osteoclastogenesis.

Disclosure of Interests: : None declared

DOI: 10.1136/annrheumdis-2019-eular.3479

FRI0528

HIGH INTENSIVE THERAPEUTIC LOWERING OF SYSTEMIC CHOLESTEROL DOES NOT AMELIORATE OA DEVELOPMENT IN KNEE JOINTS OF HUMANIZED DYSLIPIDEMIC MICE

Yvonne van Gemen¹, Anne Kozijn^{2,3,4}, Marianne Pouwer^{2,5}, Nik Kruisbergen¹, Martijn van den Bosch¹, Arjen Blom¹, Elsbeth Pieterman², Harrie Weinans^{3,6}, Reinout Stoop², Hans Princen², Peter van Lent¹. ¹Radboud university medical center, Experimental Rheumatology, Nijmegen, Netherlands; ²TNO, Metabolic Health Research, Nijmegen, Netherlands; ³UMC Utrecht, Department of Orthopaedics, Utrecht, Netherlands; ⁴UMC Utrecht, Department of Rheumatology and Clinical Immunology, Utrecht, Netherlands; ⁵Leiden UMC, Department of Cardiology, Leiden, Netherlands; ⁶Delft University of Technology, Department of Biochemical Engineering, Delft, Netherlands

Background: High systemic cholesterol levels have been associated with osteoarthritis (OA) development and lowering cholesterol using statins has been suggested as a potential treatment for OA¹. Recently, novel therapeutic high-intensive cholesterol-lowering treatment has been shown to regress Western-type diet (WTD)-induced atherosclerosis in dyslipidemic APOE*3Leiden.CETP mice, a translational model with a human-like lipoprotein metabolism².

Objectives: Here, we investigated the potency of these therapeutic cholesterol-lowering strategies to attenuate OA development in dyslipidemic APOE*3Leiden.CETP mice.

Methods: Female mice (n=13-16 per group) were fed a cholesterol-supplemented WTD for 38 weeks. After 13 weeks, mice were matched into a baseline group (sacrificed at t=13w) and 5 groups that received WTD alone or with treatment for 25 weeks: atorvastatin alone (A), in combination with PCSK9 inhibitor alirocumab (AA) or ANGPTL3 inhibitor evinacumab (AE) or triple treatment (AAE). Plasma lipids were monitored to assess metabolic dysfunction. Knee joints were analysed for cartilage degradation, synovial inflammation and osteophyte formation. Aggrecanase activity and S100A8 expression were determined using immunohistochemistry.

Results: Systemic administration of cholesterol-lowering interventions resulted in a significant reduction of body weight (A: -16%; AA: -8%; AE: -12%; AAE: -18% at end point) without changes in food intake. WTD-feeding manifested itself in dyslipidemia, with high cholesterol levels that were significantly reduced after administration of therapeutic cholesterol-lowering interventions (A: -46%; AA: -74%; AE: -74%; -AAE: 86% at end point). Using detailed OARSI scoring, dyslipidemic mice showed a mild but significant increase in cartilage degeneration at end point (7.8 ± 1.9) compared to baseline controls (3.8 ± 1.8 , 2.1-fold increase, $p=0.001$), and a strong 52-fold increase in NITEGE staining, representing proteolytic activity by aggrecanases³. However, therapeutic cholesterol lowering did not ameliorate further progression of cartilage destruction. This was supported by comparable NITEGE staining in all treatment groups at end point. Dyslipidemic APOE*3Leiden.CETP mice developed minor synovial inflammation which was not affected by cholesterol-lowering interventions. Alarmin S100A8, a marker for macrophage activation, showed minor expression in the synovial lining of all treatment groups, supporting the absence of joint inflammation in this model⁴. Finally, we determined whether high plasma cholesterol levels promoted osteophyte formation. The total number of osteophytes and osteophyte maturation stage was comparable between all groups despite reduction of systemic cholesterol levels.

Conclusion: Therapeutic cholesterol-lowering interventions did not slow the progression of cartilage degradation and osteophyte formation in dyslipidemic APOE*3Leiden.CETP mice with minor joint inflammation. These findings suggest that therapeutic cholesterol-lowering interventions in the absence of local inflammation within the knee joint cannot prevent progression of OA.

REFERENCES:

- [1] Gierman, LM, Ann Rheum Dis, 2014; 73, 921-927.
- [2] Dewey, F.E., New Engl J Med 2017; 377, 211-221.
- [3] van Meurs JB, Arthritis Rheum 42, 1999; 42, 1128-1139.
- [4] van Lent PL, Arthritis & Rheumatism 2012; 64, 1466-1476.