## 20 A HIGH CHOLESTEROL DIET CAUSES FAT UPTAKE BY SYNOVIAL LINING MACROPHAGES AND ENHANCES JOINT INFLAMMATION AND CARTILAGE DESTRUCTION DURING EXPERIMENTAL ARTHRITIS

P L E M van Lent, W de Munter, A B Blom, A W Sloetjes, W B van den Berg *Department of Rheumatology, Radboud University Nijmegen, Medical Centre, Nijmegen, The Netherlands*

10.1136/annrheumdis-2011-201237.20

**Background and objectives** Earlier studies have shown that synovial lining macrophages are crucial in mediating joint inflammation and cartilage destruction during experimental arthritis.[1] Oxidised low-density lipoprotein (ox-LDL) has been shown to activate macrophages which may enhance joint inflammation and cartilage destruction. Uptake of ox-LDL by macrophages is clearly seen in atherosclerotic lesions of mice made deficient for the LDL receptor which were given a high fat diet.

The aim of the present study was to investigate the effect of a high fat diet in LDLr$^{-/-}$ mice on uptake of fat by synovial lining macrophages and development of joint inflammation and cartilage destruction during experimental arthritis.

**Material and methods** LDLr–/– mice were given a high fat or a normal fat diet for 50 days. Experimental arthritis was induced by giving 0.2 ml antiserum KXRN serum systemically twice at alternate days. Arthritis was scored macroscopically using an arbitrary score and histologically using sections of forepaws. Sections were stained with H&E or safranin-O. Cartilage destruction was measured as either proteoglycan depletion, cartilage matrix erosion and chondrocyte death. MMP mediated neoepitopes were determined using immunolocalisation and VDIPEN antibodies. Bone marrow derived macrophages were stimulated by oxidised LDL. Expression of receptors was determined using RT-PCR and FACS analysis. Protein levels of cytokines was measured using Luminex.

**Results** Induction of KxRN arthritis in LDLr$^{-/-}$ mice given a high fat diet for 50 days showed a higher joint inflammation in the wrist of the fore-paws when compared to LDLr$^{-/-}$ which received a normal diet. At days 2, 5 and 12, the macroscopic score was 171%, 46% and 63% higher respectively. Histology of forepaws taken at day 12 after arthritis induction showed significantly higher amounts of mainly PMN as seen after immunostaining with NIMPR14 antibody. When bone-marrow macrophages were stimulated with ox-LDL for 24 h, protein levels of PMN attracting chemokine KC was significantly higher whereas that of macrophage attracting chemokine MCP-1 was comparable to the production by control macrophages. Serum levels of triglyceride and cholesterol were significantly higher in high fat treated LDLr$^{-/-}$ mice when compared to LDLr$^{-/-}$ mice fed with a normal diet. Cryostate sections of total knee joints stained with red oil showed strong accumulation of fat within the lining macrophages which was much lower in the LDLr$^{-/-}$ fed with a normal diet. At day 12 after arthritis induction, serum levels of interleukin 6 (IL-6) were significantly higher in high-fat diet group whereas levels of IL-1β and TNFα were undetectable. Cartilage destruction measured in four different distal carpals (1–4) of the wrist was significantly higher in the fat-rich treated group. Proteoglycan depletion, erosion of the cartilage matrix and chondrocyte death were respectively 65%, 333% and 283% higher when compared to the normal diet group. In line with that a significantly higher VDIPEN expression was observed in the cartilage layers of the high fat diet group.

**Conclusions** LDLr$^{-/-}$ mice given a high fat diet accumulate fat within synovial lining macrophages and exhibit enhanced joint inflammation and cartilage destruction during experimental arthritis.

### REFERENCE

1. **Blom AB**. Crucial role of macrophages in matrix metalloproteinase-mediated cartilage destruction during experimental osteoarthritis: involvement of matrix metalloproteinase 3. *Arthritis Rheum* 2007;**56**(1):147–57.