Background: Rheumatoid arthritis (RA) has been associated with atherosclerosis and cardiovascular (CV) disease. 18F-fluorodeoxyglucose positron emission tomography/computed tomography (18FDG-PET/CT) is suitable to detect synovial and vascular inflammation simultaneously by 18FDG-PET/CT. Tofacitinib has been used to effectively treat RA.

Objectives: We wished to assess the effects of tofacitinib treatment on synovitis and vascular inflammation simultaneously by 18FDG-PET/CT.

Methods: Thirty RA patients with active disease were treated with either 5mg bid or 10mg bid tofacitinib and evaluated at baseline and after 6 and 12 months. We determined DAS28, CRP, IgM rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) levels. All patients underwent 18F-fluorodeoxyglucose positron emission tomography/computed tomography (18FDG-PET/CT) in order to determine vascular and synovial inflammation in five aortic segments and five articular regions, respectively. In the joints, mean (SUVmean) and maximum standard uptake values (SUVmax), while in the aorta, mean (TBRmean) and maximum target-to-background ratios (TBRmax) were determined. Carotid intima-media thickness (IMT), arterial stiffness (PWV) and endothelial dysfunction (FMD) were determined by ultrasound.

Results: One-year tofacitinib treatment significantly attenuated vascular and synovial inflammation as visualized by PET/CT. Articular SUVmean (p=0.010), as well as aorta SUVmax (p<0.001) significantly decreased over time. Synovial inflammation as determined by PET/CT variably and positively associated with anti-COP, RF, CRP, ApoB, Lipoprotein A (LpA), IMT and PWV. Vascular inflammation (TBRmean) inversely correlated with HAQ and positively with ESR, ApoA, and PWV. Uni- and multivariable analyses suggested that articular SUV values were independently associated with CRP, ApoB, LpA, IMT and PWV, while aortic TBR was determined by HAQ and PWV.

Conclusion: 18FDG-PET/CT is suitable to simultaneously assess synovial and vascular inflammation in RA. One-year tofacitinib treatment dampened inflammation. PET/CT changes were associated with markers of systemic inflammation, atherosclerotic lipids, carotid atherosclerosis and arterial stiffness.

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Disclosure of Interests: None declared.
IgG autoantibody levels (P<0.05) towards another antigen, dual specificity mitogen-activated protein kinase kinase 6 (MAP2K6), were also observed in ACPA-seronegative subjects compared to ACPA-seropositive and controls. In contrast, we found significantly higher IgG autoantibody levels (P<0.05) in ACPA-seropositive individuals compared to ACPA-seronegative and controls toward two antigens, anosmin-1 (ANOS-1) and muscle related coiled-coil protein (MURC). ANOS-1 shows also significantly higher IgG reactivity frequency in ACPA-seropositive individuals compared to ACPA-seronegative and controls (22%, 9% and 6% respectively; P<0.05). Interestingly, three out of the four antigens discovered to be associated with the ACPA status in early RA are highly expressed in lungs and heart, two of the main extraarticular sites affected in RA. No significant differences were observed at IgA levels for any of the antigens analyzed.

Table 1. Scheme of the different phases of the study, the features within each phase and the results. The reactivity to four antigens allows to distinguish ACPA-seronegative (ACP(-)), ACPA seropositive (ACP(+) and controls.

Conclusion: Upon further validation in other early RA sample cohorts, our data suggest the measurement of these four autoantibodies may be useful for the early diagnosis of ACPA-seronegative RA and give insight into the pathogenesis of the different RA subsets.

Characteristics from table content including title and footnotes:

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FIBRIN DEPOSITION IS AN ACTIVE TRIGGER OF CARTILAGE DEGENERATION IN RHEUMATOID ARTHRITIS

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Background: Fibrin(ogen) maintains inflammation in various disorders but has never been linked to cartilage damage in rheumatoid arthritis (RA) or other forms of inflammatory arthritis.

Objectives: To investigate the role of fibrin deposition on cartilage integrity in arthritis.

Methods: Fibrin deposition on knee cartilage was analyzed by immunohistochemistry in RA patients and in murine adjuvant-induced arthritis (AIA). In chondrocytes, fibrinogen expression (Fg), fibrin(ogen) and procoagulant activity were evaluated by qRT-PCR and turbidimetry respectively. Fibrin-induced catalytic genes were assessed by qRT-PCR in chondrocytes. Fibrin-mediated chondro-synovial adhesion (CSA) with subsequent cartilage tears was studied in co-cultures of human RA cartilage with autologous synoviocytes, in the AIA model, and by MRI. The link between fibrin and calcification was examined in human RA cartilage stained for calcific deposits and in vitro in fibrinogen-stimulated chondrocytes.

Results: Fibrin deposition on cartilage correlated with the severity of cartilage damage in human RA explants and in AIA wildtype (WT) mice, while fibrinogen deficient (FG(-/-) mice were protected. Accordingly, fibrin upregulated catalytic enzymes (AdamsS and Mmp13) in chondrocytes. Secondly, CSA was present in fibrin-rich and damaged cartilage in AIA WT but not in FG(-/-) mice. In line, autologous human synoviocytes, cultured on RA cartilage explants, adhered exclusively to fibrin-positive degraded areas. Gadolinium-enhanced MRI of human joints showed contrast-enhancement along cartilage surface in RA patients but not in controls. Finally, fibrin co-localized with calcification in human RA cartilage and triggered chondrocyte mineralization inducing pro-calcification genes (Anx5, Pit1, Pcol1 and cytokine (IL-6). Although at a much lesser extent, we observed similar fibrin-mediated mechanisms in osteoarthritis (OA).

Conclusion: Fibrin deposition directly impacts on cartilage integrity via induction of catabolism, mechanical stress, and calcification. Potentially, fibrin is a key factor of cartilage damage occurring in RA as a secondary consequence of inflammation.

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NAD+ BOOSTERS REESTABLISH THE ALTERED NAD+ METABOLISM OF LEUKOCYTES FROM RHEUMATOID ARTHRITIS PATIENTS IMPROVING THEIR OXIDATIVE, APOTOTIC AND INFLAMMATORY STATUS

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Background: NAD+ is an important co-factor and a colocalizer for multiple cellular processes that exhibit antioxidant, anti-apoptotic and anti-inflammatory properties. Pre-clinical studies in animal models of Rheumatoid Arthritis (RA) have demonstrated the therapeutic potential of NAD+ boosters in the control of the disease activity. However, to date no studies have been set up to evaluate the NAD+ metabolism and the therapeutic effects of NAD+ boosters in RA patients.

Objectives: 1- To study the NAD+ metabolism in RA patients and its association with key clinical features. 2- To evaluate the effect of anti-TNF therapy in the NAD+ metabolism. 3- To analyze the beneficial effects of NAD+ boosters in leukocytes from active RA patients.

Methods: Plasma and PBMCs were purified from 100 RA patients and 50 healthy donors (HDs). Moreover, an additional cohort of 50 RA patients treated with Anti-TNF therapy was analyzed before and after 6 months of treatment. NAD+ levels were determined by using the NAD/NADH-Glo Assay. NAD+-consuming genes expression were analyzed by RT-PCR. In parallel, PBMCs from eight HDs and eight active RA patients were treated ex vivo with 1mM of NAD+ boosters including nicotinamide (NAM), nicotinamide riboside (NR), and nicotinamide mononucleotide (MN). After 24 hours, intracellular reactive oxygen species (ROS) levels (DFCHDA) and the percentage of apoptotic PBMCs (annexin V/PI) were assessed by flow cytometry. Lastly, a panel of key pro-inflammatory genes were evaluated by using RT-PCR.

Results: NAD+ and NADH levels were significantly reduced in plasma and PBMCs of RA patients compared with HDs and directly related to disease activity (DAS28, CDAI, SDAI). Accordingly, the expression levels of genes involved in the consumption of NAD+ such as SIRT1, CD38 and PARP-1 were found up-regulated in PBMCs from RA patients. Anti-TNF therapy for 6 months restored the altered NAD+ levels towards those showed by HDs. Furthermore, the clinical response promoted by Anti-TNF therapy (changes in DAS28) correlated with changes in NAD+ levels. The in vitro treatments of PBMCs isolated from active RA patients with NAD+ boosters significantly increased the NAD+ levels and promoted a deep reduction of intracellular ROS levels, the percentage of apoptotic cells and the expression levels of key inflammatory mediators, such as IL-6, IL-8, IL-18, TNF-a, CCL2, IL-23, and STAT-3.

Conclusion: NAD+ metabolism is altered and associated with the disease activity of RA patients, involving both, reduced NAD+ levels and increased expression of NAD+-consuming genes. 2. Anti-TNF therapy restored NAD+ levels, which were directly linked to the clinical effectiveness. 3. NAD+ boosters reduced the oxidative, apoptotic and inflammatory profiles of RA leukocytes through the parallel increase of intracellular NAD+ levels. Thus, NAD+ boosters might be considered novel therapeutic tools for RA patients.

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ANTI-ACYETLATED PROTEIN ANTIBODIES IN RHEUMATOID ARTHRITIS (RA): CLUES FOR THE STARTING POINT OF AUTOIMMUNE RESPONSES IN RA

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Background: Rheumatoid arthritis (RA) is characterized by autoantibodies such as rheumatoid factor (RF) and anti-modified protein autoantibodies (AMPAs) like anti-citrullinated protein antibodies (ACPA) and anti-carbamylated protein antibodies.