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THU0065

RESULTS OF TREATMENT OF ARTHROSCOPIC AND TRADITIONAL SYNOVECTOMY OF THE KNEE JOINT IN RHEUMATOID ARTHRITIS

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Background: Rheumatoid arthritis is a systemic inflammatory autoimmune disease of connective tissue with a predominant joint injury that occurs at any age, more often in women. It is characterised by a chronic course with periods of exacerbations and remissions

Objectives: To evaluate the results of arthroscopic and traditional synovectomy of the knee joint in patients with rheumatoid arthritis

Methods: The study involved 48 patients, 29 of them were women and 19 men, aged from 25 to 65 years old, who had a chronic synovitis of the knee joints. It was implemented at the department of traumatology, orthopaedics and GPH with neurosurgery of Tashkent Medical Academy and 1-Republic Clinical Hospital. In all patients, on the background of basic therapy and intraarticular injections of SCS, a persistent recurrent synovitis was formed within a few months. Sixteen patients underwent sinocapsulectomy (SCE) with the traditional method. 32 patients underwent arthroscopic synovectomy (ASE), for which the standard basic arthroscopic technique Dyonics (Smith and Nephew) was used. The functional condition of the knee joint before and after the operation was assessed using the KOOS scale (Knee and Osteoarthritis Outcome Score)

Results: The study showed that movements in the operated joint were allowed 3–5 hours after the operation, from the first day, isometric exercises were prescribed, active movements in the knee joint before the onset of pain. Results of treatment in terms of up to 3 months were tracked in all 48 patients. The degree of intraarticular changes determined by arthroscopy was evaluated according to the Outerbridge classification. In patients after SCE, pain in the joint, limiting the amplitude of motion, crunching during movement were noted. After ASE, there was a significant improvement in the function and condition of the knee joint: patients could walk for longer distances without additional support, did not experience discomfort while walking the stairs, complaints of pain, and no swelling. Repeated ASE with tunnelling was required in 2 patients with grade III chondromalacia

Conclusions: Thus, the SCE of the knee is indicated if the conservative treatment of recurrent synovitis in RA is unsuccessful for a long time. The ASE should be performed in the early stages of the RA, which drastically reduces the activity of the pathological process, makes it possible to maintain the functional capacity of the joint, and the timely adequate administration of the basic therapy allows the maximum achieved long-term functional result to be maintained for the longest time and reduces the risk of relapse and the need for repeated operations

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THU0066

CIRCULATING MIRNAS AS POTENTIAL BIOMARKERS OF DISEASE AND CARDIOVASCULAR RISK IN RHEUMATOID ARTHRITIS PATIENTS

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Background: Circulating miRNAs have been proposed as attractive candidates as both diagnostic and prognostic biomarkers in various diseases, including a spectrum of autoimmune and cardiovascular conditions. Yet, the contribution of

circulating miRNAs to the cardiovascular pathogenesis of Rheumatoid Arthritis (RA) patients and their potential role as biomarkers are still unknown.

Objectives: To identify circulating miRNAs as potential biomarkers of disease features and cardiovascular (CV) risk in RA.

Methods: Plasma samples of 48 healthy donors (HDs) and 124 RA patients were collected. In the discovery phase, an array of 2083 human miRNAs was performed by using HTG EdgeSeq miRNA Whole Transcriptome Assay (Next generation sequencing) in 9 plasma samples (3 HDs, and 6 RA patients). Then, differentially expressed miRNAs, were selected and validated by RT-PCR in the whole cohort of patients and HDs. Potential targets of the validated miRNAs were identified by using Ingenuity Pathway Analysis (IPA) software and analysed at protein levels (Multiplex Assay). Correlation and association studies of altered miRNAs with analytical and clinical variables were also performed.

Results: The miRNA whole Transcriptome assay showed that 360 miRNAs were differentially expressed in RA patients in relation to HDs, including 261 upregulated and 97 downregulated. Functional classification (IPA) demonstrated that deregulated miRNAs were mainly involved in processes such as inflammatory response, connective tissue development and function, haematological disease, tissue development, and immunological disease. Nine microRNAs, selected among the most differentially expressed in the array, were selected for validation in all the subjects recruited (miR-299, miR-567, miR-4293, miR-135b, miR-6816, miR-346, miR-143, miR-199a, miR-106a, miR-148b). *In silico* analyses showed that these miRNAs had potential targets related to cytokine signalling, atherosclerosis pathway and intracellular signalling. The altered levels of selected miRNAs and its putative target proteins were validated in the whole cohort of patients.

A number of serum miRNAs in all the RA patients analysed were found inter-related and associated to autoimmunity (positivity for anti-CCPs and RF), bone erosion, inflammation (CRP, ESR, TNFα, IL6, IL8, IFN and IL-2), and evolution time. We could further identify a specific signature of four miRNAs (miR143, miR106, miR148b and miR567) that identified RA patients that had suffered previous CV events and specifically associated with the increase in the carotid intima-media thickness (CIMT) and with 'Framingham CV risk factors' such as diabetes, obesity or dyslipidemia.

Conclusions: We have branded novel and specific circulating miRNAs related to disease features and CV risk in RA patients, including, their autoimmune and inflammatory profile, the presence of Framingham risk factors and incipient atherosclerosis. These circulating miRNAs might be thus considered useful tools for the management of the disease in this autoimmune condition.

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THU0067

ASSOCIATION OF HIGH TITERS OF ANTI-CARBAMYLATED PROTEINS ANTIBODIES WITH DECREASED BONE MINERAL DENSITY IN EARLY ARTHRITIS PATIENTS

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Background: Rheumatoid arthritis (RA) has a negative impact on bone homeostasis, in which multiple inflammatory mediators are involved together with the anti-citrullinated proteins antibodies (ACPA). These antibodies are able to promote osteoclastogenesis and bone loss even before the onset of synovitis. Accordingly, ACPA are associated with the three aspects of bone loss: joint bone erosion, juxta-articular bone loss and, as recently demonstrated¹, decreased bone mineral density (BMD). Other RA specific autoantibodies, the anti-carbamylated protein antibodies (anti-CarPA), are associated with the presence, severity and progression of erosions with independence of ACPA. However, their implication in the other aspects of bone loss has not been studied.

Objectives: To evaluate the association of anti-CarPA with BMD in a cohort of early arthritis (EA) patients.

Methods: Clinical data and samples were obtained at the first visit of 548 patients from the Princesa Early Arthritis Register Longitudinal (PEARL) study, which recruits patients within one year from arthritis onset. BMD was assessed by dual-energy x-ray absorptiometry (Hologic QDR-4500, Elite, Mass, USA) at the lumbar spine (LS), total hip (TH) and metacarpophalangeal (MCP) joints. BMD was considered as Z-scores, except for MCP due to lack of reference data. Anti-CarPA were determined by ELISA using carbamylated fetal calf serum. The ELISA results were considered as negative, below the 98 percentile of healthy controls, low-positive, below the median of positive patients, and high-positive, otherwise. Data were analysed with linear regression including sex, age, BMI, and menopause as covariates.

Results: Anti-CarPA were positive in 25.9% of the EA patients. The positive patients did not show significant differences in BMD with the negative patients.

However, this lack of association was due to the similarity of negative and low-positive patients, because the high-positive patients showed significant decrease of BMD at LS ($\beta = -0.39$, $p = 0.01$) and TH ($\beta = -0.30$, $p = 0.02$). Nevertheless, we did not found significant association at the juxta-articular bone of the MCP joints. Given the overlap between anti-CarPA and ACPA, we included the two autoantibodies in multivariate analysis. The association with BMD was significant only in the ACPA positive/anti-CarPA high-positive subgroup at LS and TH ($p = 0.007$ and 0.005 , respectively). In addition, the coefficients of regression were similar between the ACPA positive/anti-CarPA high-positive and the ACPA negative/anti-CarPA high-positive subgroups ($\beta = -0.50$ vs. -0.52 at LS, and $\beta = -0.37$ vs. -0.30 at TH).

Conclusions: We found significantly lower BMD at LS and TH in the patients with high anti-CarPA titers. These associations seem to be independent from the presence of ACPA, suggesting that anti-CarPA could contribute to systemic bone loss in EA patients.

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THU0068 IDENTIFICATION AND VERIFICATION OF BIOMARKER CANDIDATES FOR MONITORING RHEUMATOID ARTHRITIS ACTIVITY BY MASS SPECTROMETRY

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Background: Rheumatoid arthritis (RA) is a long-lasting inflammatory autoimmune disorder that ultimately leads to the destruction of joint architecture. The activity of this disease is measured by the assessment of clinical symptoms.

Objectives: To apply a proteomic strategy to find serum biomarkers able to discriminate patients with different RA activities.

Methods: To facilitate the complex measurement of serum by proteomics, a simple, fast and reproducible albumin-specific depletion method using ethanol was optimised and applied to the samples employed in this study. 80 samples from the IMID consortium, classified according to the DAS28 score into low activity⁴⁰ and high activity⁴⁰ were analysed by mass spectrometry. Four independent pools of the high RA activity samples (10 samples per pool) and 4 pools of the low RA activity samples were firstly albumin-depleted, and then the remnant serum proteins were digested and differentially labelled with iTRAQ 8-plex reagents. Subsequently, the 8 labelled pools were combined and cleaned using StageTips-C18. Finally, the pool mixture was fractionated by HPLC (Zorbax-C18) and the resulting fractions were analysed by nanoLC-MS/MS using MALDI-TOF/TOF, TripleTOF and LTQ-Orbitrap.

Results: The mass spectrometry analysis led to the identification of 186 proteins. In this screening step, the abundance of 9 proteins was found to be significantly different between patients with high (H) and low (L) RA activity. Orthogonal experiments, using Western Blot, protein bead arrays and Multiple Reaction Monitoring (MRM) with synthetic heavy-labelled peptides, were conducted in order to verify some of these biomarker candidates of RA activity. The results obtained from the verification phase, conducted by MRM on 50 samples from the same cohort, show a decrease of Apolipoprotein B (ratio H/L=0.84, $p = 0.00$), Histidine Rich Glycoprotein (ratio H/L=0.86, $p = 0.01$) and Plasma protease C1 inhibitor (ratio H/L=0.84, $p = 0.02$). Furthermore, this verification phase shows also an increase of Haptoglobin (ratio H/L=1.34, $p = 0.01$) and Serum Amyloid A1 (ratio H/L=1.64, $p = 0.05$), in accordance with that observed in the screening. These proteins are related with the RA process and the effects caused by this type of disease (inflammation and immune disorder in joints).

Conclusions: In this proteomic study, 5 proteins were found to be quantitatively altered between patients with high and low RA activity using shotgun and targeted mass spectrometry.

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THU0069

IN RA, BECOMING SERONEGATIVE OVER THE 1ST YEAR OF DMARD TREATMENT DOES NOT TRANSLATE TO BETTER CHANCES OF SUSTAINED DRUG-FREE REMISSION IN THE LONG-TERM

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Background: In rheumatoid arthritis (RA), autoantibodies are a reflection of the underlying B cell autoimmunity and an important predictor of long-term outcome. Baseline seropositivity is a poor prognostic factor for sustained drug-free remission (SDFR). However, autoantibody levels may change and patients may become seronegative under treatment. It is unknown how often this happens and whether some autoantibodies (depending on isotype use or antigen recognition) disappear more often than others. Furthermore, it is unclear whether becoming seronegative early in disease, indicating disappearance of serological autoimmunity, improves chances of SDFR.

Objectives: To longitudinally characterise the levels and presence of autoantibodies in RA patients and to investigate whether changes in these levels and/or presence associates with SDFR.

Methods: In sera of 399 seropositive RA patients in the IMPROVED study¹, we measured, at 4-month-intervals over the first year of treatment: IgG, IgM, and IgA isotypes for anti-cyclic citrullinated peptide-2 (anti-CCP2) and anti-carbamylated protein antibodies (anti-CarP), IgM and IgA for rheumatoid factor (RF), and IgG autoantibodies against 4 citrullinated and 2 acetylated peptides. We investigated whether changes in antibody levels and seroconversion from positive to negative for each individual antibody was favourable for SDFR (drug-free DAS44 <1.6 lasting ≥ 1 year until last follow-up).

Results: For all 14 antibodies, median levels decreased significantly between baseline and 4 months and then stabilised. Most seroconversion to negative happened within the first 4 months of treatment (with prednisone and methotrexate), after which some patients converted back to seropositive. The prevalence of seroconversion varied substantially depending on the autoantibody. The percentage of patients who were seropositive at baseline and became seronegative by 12 months varied substantially depending on the autoantibody: 2% (anti-CCP2 IgG) to 66% (anti-CarP IgA) (see figure 1). We hypothesised that greater level decreases and seroconversion to negative might be favourable for the long-term outcome SDFR, but surprisingly, greater median decreases in levels were not associated with higher chance of SDFR for any antibody. Furthermore, using Chi-squared tests, we found no evidence that rates of SDFR were higher in patients who seroconverted to negative compared to those who stayed seropositive, for any of the 14 antibodies analysed (see figure 1).

Abstract THU0069 – Figure 1. Percentage of patients reaching SDFR (drug-free DAS44 <1.6 lasting ≥ 1 year until last follow-up), separated by whether patients