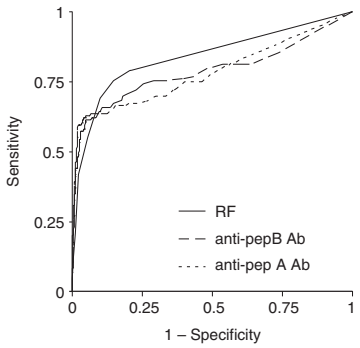
Figure 1



ROC curves.

Results The following diagnoses were made: definite RA ($n = 144$), non-RA ($n = 629$), undifferentiated ($n = 156$), and lost to follow up ($n = 74$). The first two groups were used to determine sensitivity, specificity, and positive predictive value (PPV). ROC curve analysis (Fig. 1) showed a higher area under the curve for RF than for anti-pepA and anti-pepB antibodies (0.839 versus 0.784 and 0.788, respectively), but in the high specificity region anti-pepA and anti-pepB antibodies performed better than RF (Table 1).

Table 1

Diagnostic performance of serum markers using different cut offs

Antibody	Cutoff	Sensitivity (%)	Specificity (%)	PPV (%)
PepA	Low	63.6	90.6	60.7
PepB		64.3	90.0	59.0
RF		69.2	90.1	61.5
PepA	Intermediate	62.9	95.1	74.4
PepB		61.5	95.1	73.3
RF		55.2	94.6	69.9
PepA	High	58.7	98.1	87.5
PepB		48.3	98.1	85.2
RF		42.0	97.8	81.1
PepA	Very high	41.3	99.0	90.8
PepB		37.1	99.0	89.8
RF		21.0	99.0	83.3

Conclusion When high specificity is required, anti-pepA and anti-pepB antibodies have a markedly higher sensitivity than RF. The highest PPV are found when ACPA are very high.

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Citrullinated proteins in arthritis: presence in joints and effects on immunogenicity

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Arthritis Res Ther 2004 **6(Suppl 1):**18 (DOI 10.1186/ar1060)

Background Autoantibodies (Ab) directed against citrulline (Cit)-containing proteins have a specificity of nearly 100% in rheumatoid arthritis (RA) patients. The presence of these markers early in disease, even before clinical onset, and the observation that these autoantibodies are produced locally in the pannus suggest an involvement in the pathogenesis. The targeted epitopes are generated by deimination, a post-translational modification catalyzed by the enzyme peptidyl arginine deiminase.

Objective Our aim was to analyze the presence of Cit-proteins and fibrinogen in the joints at different time points in collagen-induced arthritis (CIA) in rats and to investigate how citrullination of an autoantigen affects its immunogenicity.

Methods Synovial tissue sections from DA rats were stained for expression of citrulline and fibrinogen. Lew1AV1 rats were immunized with Cit-rat serum albumin (RSA) or unmodified RSA, and antibody and T-cell responses were evaluated.

Results Citrulline was detected in arthritic joints from disease onset and increased expression was noted as disease progressed into a more chronic state. Naïve rats or time points before arthritis onset were negative for citrulline-specific staining. Infiltrating cells, as well as the cartilage surface, stained positive for citrulline, although the major source of citrullinated proteins appeared to be fibrin depositions. A specific Cit-RSA T-cell response was observed in animals challenged by Cit-RSA. In contrast, no response was recorded when RSA was used as a stimulus. The IgG response revealed not only a response toward the modified protein but also cross-reactivity to the unmodified form of RSA.

Conclusion In CIA, joint inflammation precedes the presence of Cit-proteins and citrullination increases immunogenicity of an autoantigen. Our results suggest that citrullination is induced by inflammation and might be contributing to the development of autoreactive T and B cells.

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Antifilaggrin antibodies in serum and synovial fluid samples of patients with rheumatoid arthritis show similar reactivity pattern towards citrulline containing peptides

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Arthritis Res Ther 2004 **6(Suppl 1):**19 (DOI 10.1186/ar1061)

Background Antifilaggrin antibodies are highly specific serological markers of rheumatoid arthritis (RA). They have been shown to comprise a heterogeneous population of antibodies directed at citrullinated peptides. Recent studies suggest that the site of the initial antigenic trigger where these autoantibodies are produced can be localized to the synovial tissue.

Objective The aim of this study was to compare the recognition patterns of antibodies in paired serum and synovial fluid samples of RA patients toward citrullinated peptide sequences to investigate whether or not they comprise the same antibody population.

Methods Arginine-rich peptide sequence corresponding to human profilaggrin (amino acid residues 306–324) and sequences with citrulline substitution at different positions were synthesized by mutipin peptide synthesis on solid support. Completely citrullinated variant of the 19-mer peptide and shortened sequences were also produced. The reactivity of these peptides with paired sera and synovial fluid samples of RA patients were determined ($n = 25$). Results were evaluated statistically using the paired t test.

Results and Conclusion The results (Table 1) show that the 12–19 amino acid long epitopes are recognized by homogeneous antibody population present in serum and synovial fluid, whereas the reactivities toward short citrullinated sequences differs significantly.

Acknowledgement This work was supported by the Hungarian grant: OTKA T037876.