Advanced glycation end product pentosidine is not a relevant marker of disease activity in patients with rheumatoid arthritis

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Abbreviations: RA, rheumatoid arthritis; OA, osteoarthritis; AGE, advanced glycation end products; COMP, cartilage oligomeric matrix protein; CRP, C-reactive protein; DAS 28, Disease Activity Score 28; HAQ, Health Assessment Questionnaire; HPLC, high performance liquid chromatography; ELISA, enzyme-linked immunosorbent assay

SUMMARY

Advanced glycation end product (AGE) pentosidine has previously been demonstrated in different tissues and body fluids. It was suggested as a novel marker for evaluating the disease activity in rheumatoid arthritis (RA). In this study we analyzed association between pentosidine and markers of inflammation, cartilage turnover, immune response, and disease status of RA. Using HPLC, we analyzed pentosidine in serum and synovial fluid from 39 patients with RA and in serum from 38 healthy controls. Cartilage oligomeric matrix protein (COMP) and antibodies to CCP (anti-CCP) were measured by ELISA. Clinical disease status was assessed by Disease Activity Score 28 (DAS28) and functional status by Health Assessment Questionnaire (HAQ). We demonstrated significantly higher serum levels of pentosidine in RA patients in comparison with controls. Pentosidine in serum significantly correlated with pentosidine in synovial fluid. Serum pentosidine levels were associated with erythrocyte sedimentation rate ($p<0.03$) but not with CRP, COMP, anti-CCP antibodies, DAS28, or HAQ. In contrast to previous studies, we could not show any correlation of pentosidine levels with inflammatory status, clinical disease activity, markers of immune response, or cartilage breakdown. However, rather than markers of disease activity, AGEs can be suggested as important players participating in joint destruction.

Key words: Pentosidine, advanced glycation end product (AGE), rheumatoid arthritis, cartilage oligomeric matrix protein (COMP), anti-CCP antibodies

INTRODUCTION

Pentosidine represents one of the well-characterized members of advanced glycation end products (AGEs) that are formed during spontaneous reaction of pentoses with free amino groups such as lysine and arginine. It is apparent that beside non-enzymatic glycation, oxidative stress, and inflammatory processes significantly accelerate formation of AGEs. Pentosidine has been found in a variety of human tissues where it forms both adducts and intermolecular cross-links, which are suggested to be the link between tissue damage and aging process (Sell and Monnier 1989). AGEs accumulation is associated with several age-related diseases including diabetes mellitus (Dyer et al 1993, Monnier et al 1992), renal failure (Miyata et al 1996), or Alzheimer disease (Smith et al 1994).

The highest accumulation of AGEs was observed in tissues with long-lived proteins such as in articular cartilage collagen (Takahashi et al 1994, Verzijl et al 2000). This phenomenon is proposed to be responsible for the modification of both biochemical and mechanical properties of the hyaline cartilage during aging (Verzijl et al 2003). In addition to articular cartilage (Takahashi et al 1994), higher accumulation of AGEs has also been detected in synovial tissue (Drinda et al 2002), serum, urine, and synovial fluid in patients with rheumatoid arthritis (RA) (Chen et al 1999, Chen et al 1998, Miyata et al 1998, Takahashi et al 1997). RA represents a chronic inflammatory autoimmune disease affecting joints as well as extraarticular tissues. Cartilage destruction and bone erosion, the main phenomena of RA pathology, are induced by hyperplastic synovium containing activated synovial fibroblasts and immune cells (Karouzakis et al 2006, Stanczyk et al 2006). These cells can trigger production of reactive oxygen species thereby increasing oxidative stress that is supposed to contribute to the pathogenesis of RA (Hitchon and El-Gabalawy 2004). It represents a vicious cycle contributing to higher levels of pentosidine in joint tissues and body fluids in RA patients as mentioned above. Moreover, higher levels of pentosidine in body fluids in RA patients correlated significantly with inflammatory markers including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), white blood cell count, and platelet count, as well as with activity of the disease, making pentosidine a potential novel RA biomarker (Chen et al 1999, Chen et al 1998, Miyata et al 1998, Takahashi et al 1997).

Cartilage oligomeric matrix protein (COMP) is a non-collagenous glycoprotein that is supposed to be a marker of cartilage destruction (Neidhart et al 1997). Its increased levels in serum are good prognostic markers for further rapid joint destruction in patients with early RA (Forslind et al 1992). COMP decreases in RA patients treated with anti-TNF-α (Crnkic 2003). Last years, many studies focused on the analysis of anti-cyclic citrullinated peptides (anti-CCP) that are suggested to have diagnostic and prognostic utility for patients with RA (Vencovsky et al 2003, Raza et al 2005). Anti-CCP antibodies are strongly suggested to become a helpful new diagnostic criterion for RA that can discriminate between RA and non-RA patients in the early onset of the disease.

We have recently shown that higher serum pentosidine levels correlated significantly with marker of cartilage destruction COMP in synovial fluid from patients with knee osteoarthritis (OA) (Šenolt et al 2005). Because of this fact, we explored in this study the relationship of pentosidine with disease activity status, markers of inflammation, cartilage destruction, and anti-CCP antibodies in patients with established and active RA.

METHODS
Patients

Thirty-nine patients with active RA (32 females and 7 males, mean age 52.8 years), regularly followed at Institute of Rheumatology in Prague, Czech Republic, were enrolled to this study. Patient's characteristics are given in table one. All patients fulfilled the American College of Rheumatology (ACR) criteria for the diagnosis of RA (Arnett et al 1998). Synovial fluid was collected at the time of knee joint effusion as a part of therapeutic regimen. Blood samples were withdrawn at the time of synovial fluid aspiration. After collection, serum and synovial fluid samples were stored at –20°C. The control group, described in our previous study (Šenolt et al 2005), included 38 healthy volunteers (23 females and 15 males, mean age 58.3 years) without a history of joint disorders who agreed with blood withdrawal. Individuals with diabetes mellitus and/or abnormal serum creatinine or renal disorder were not included in this study. All individuals signed informed consents and the study was approved by the local Ethics Committee.

Clinical disease activity assessment

Clinical disease activity of RA patients was assessed by the Disease Activity Score 28 calculated according to the DAS28 formula with four variables [0.56 v (number of tender joints) + 0.28 v (number of swollen joints) + 0.7 Ln (ESR) + 0.014 (patient's assessment of disease activity)] (Prevoo et al 1995). The functional status of RA patients was assessed by the Health Assessment Questionnaire (HAQ) (Ramey et al 1992). All the RA patients were treated with low dose of glucocorticoids and disease modifying drugs (DMARDs) and none of them was treated with biologicals.

Biochemical examination

High performance liquid chromatography

As described earlier (Špacek and Adam 2002), pentosidine was measured by the high performance liquid chromatography (HPLC) combined with sensitive fluorescent detection. The method developed in our laboratory is based on reversed phase HPLC using SHIMADZU HPLC system (model: LC 10ADvp; Kyoto, Japan) operated by CLASS VP software, gradient flow of mobile phase and sensitive fluorescent detection ($\lambda_{excitation/\ emission}$ = 335/385 nm). The separation was performed using compact glass column CGC Separon SGX C18 packed with spherical silica gel particles (with diameter 7 μm) embedded with C18 (octadacyl) group, sized 150x3 mm (Tessek, Prague, Czech Republic); mobile phase (degassed with helium): 0.02 M heptafluorobutyric acid, 0.01M $(NH4)_2SO_4$ and linear gradient was given by variable concentration of acetonitrile (12.5 – 25 % ACN within 20 minutes), column temperature was 40°C, flow rate 0.5 ml/min and time of HPLC run about 30 minutes, injection 10 μl. Reproducibility of the HPLC determination itself was 98.8%.

Pentosidine synthetic standard was prepared in our laboratory by modification of the procedure provided kindly by Prof. V. M. Monnier (Case Western Reserve University, Cleveland, OH, USA). Pentosidine standard was synthesized by direct non-enzymatic reaction of carbohydrates with amino acids using poly-L-lysine (hydrobromide), D-ribose, N-α-acetyl arginine, and DETEPAC (a chelate complex former) (Sell and Monnier 1989). Sample pretreatment included acid hydrolysis (in aliquot of 12M HCl), purification and preconcentration by solid phase extraction, vacuum evaporation of excessive solvents using SpeedVac (Savant, USA) and reconstitution in mobile phase prior to the injection into HPLC.

ELISA

COMP levels were analyzed with a new sandwich ELISA, employing two monoclonal antibodies 17-C10 and 16-F12 that were purified from ascitic fluid by chromatography on a column of immobilized Protein G and concentrated by ultrafiltration. Monoclonal antibody 16-F12 was used as the first (capture) antibody, and biotinylated monoclonal antibody 17-C10 was used as the second (detection) antibody in the assay. The protocol for COMP detection was described earlier (Vilim et al 2003). Intra- and inter-assay variability was less than 7% and less than 8%, respectively.

Antibodies directed to citrullinated peptides (anti-CCP) were detected by commercially available ELISA for anti-CCP2 according to the manufacturer's protocol (Immunoscan RA, Euro-Diagnostica, Malmoe, Sweden). The results were expressed in U/ml with cut-off for normal levels at 25 IU/ml.

Statistical analysis

Values are expressed as means (SEM). The Mann-Whitney U-test was used to evaluate statistical significance of difference between two groups. Linear regression analysis was performed to find the relationship between two variables; statistical significance of the correlation was determined by means of the Spearman coefficient. P values less than 0.05 were considered statistically significant.

RESULTS:

Increased pentosidine levels in patients with rheumatoid arthritis

Pentosidine levels in serum were significantly higher in RA patients than in control individuals (155.0±20.9 vs. 97.7±4.0 nmol/l, p=0.03) (Tab.1.). Pentosidine was significantly higher in serum than in synovial fluid (155.0±20.9 vs. 85.4±11.3 nmol/l, p<0.001) and the levels in both compartments significantly correlated with each other (r=0.97, p<0.001) (Fig.1.). When the levels of pentosidine in both serum and synovial fluid in RA patients were compared with the levels measured in patients with osteoarthritis in our previous study (Šenolt et al 2005), surprisingly, only insignificant increase of pentosidine levels in RA compared to OA was observed (155.0±20.9 vs. 132.1±9.2 nmol/l, p=0.87 for serum and 85.4±11.3 vs. 70.7±3.8 nmol/l, p=0.67 for synovial fluid).

Relationship of pentosidine with the disease activity, functional status, inflammatory markers, cartilage turnover and immune response

All the patients had signs of active disease (mean DAS28=5.6), however serum pentosidine levels correlated neither with DAS28 (r=0.02) nor with HAQ (r=0.08). Pentosidine levels in serum significantly correlated with ESR (r=0.44, p<0.03) but not with CRP (r=0.04). Moreover, pentosidine levels did not correlate with leukocyte count in synovial fluid (r=0.02). Serum COMP levels (r=0.55, p<0.001), but not that in synovial fluid (r=0.03, p=0.60), correlated with age of RA patients. Age adjusted COMP levels revealed no relationship with pentosidine both in serum or synovial fluid in RA patients (data not shown). In our study group, more than 60% of RA patients were anti-CCP negative (less than 25 U/ml) and almost 40% were anti-CCP positive (51.1±6.1 U/ml). There was no significant difference between anti-CCP positive and anti-CCP negative groups with respect to serum pentosidine levels (174.3±43.5 vs. 138.7±24.8 nmol/l, respectively, p=0.45). All subjects from the control group were anti-CCP negative.

Mean of the disease duration in RA patients was 9.6 years and did not influence the pentosidine levels in serum (r=0.15) or in synovial fluid (r=0.20). Pentosidine levels in serum (r=0.23) as well as in synovial fluid (r=0.28) were not influenced by the age of RA patients. On the contrary, serum levels of pentosidine in control group correlated with age of the individuals (r=0.35, p=0.03). There were no significant differences in pentosidine levels between males and females in both RA and control groups (data not shown).

DISCUSSION

In this cross-sectional study we have not confirmed previously demonstrated relationship of higher pentosidine levels with clinical disease activity and markers of inflammation in patients with RA. Additionally, no association between pentosidine levels and markers of cartilage turnover or immune response was observed.

Recently, accumulation of AGE in articular cartilage has been proposed as a molecular mechanism by which aging may predispose to the development of OA (DeGroot et al 2004). In addition, higher body fluids levels of pentosidine were described by several research groups in patients with arthritic complaints. We have previously shown that in patients with knee OA higher levels of pentosidine correlated with a marker of cartilage breakdown COMP in synovial fluid as well as with faster radiological progression of the disease (Šenolt et al 2005, Pavelka et al 2004). An association of higher levels of pentosidine with the disease status and activity of RA patients was demonstrated (Chen et al 1999, Chen et al 1998, Miyata et al 1998, Takahashi et al 1997). Previously we found a positive correlation between pentosidine and COMP in synovial fluid in OA patients (Šenolt et al 2005), and therefore we explored whether our idea - an association between increased oxidative stress and cartilage breakdown; is also relevant to RA. However, we could not confirm this hypothesis since we did not find any correlation between body fluid levels of pentosidine in RA patients and disease activity status assessed by CRP, DAS28 or HAQ. In the studies that found positive correlations of pentosidine levels (Chen et al 1999, Chen et al 1998, Takahashi et al 1997), clinical activity was measured by different disease activity assessments such as Lansbury index, which may, at least partially, explain the distinct findings. In our study, erythrocyte sedimentation rate represented the only marker of chronic inflammation that correlated with pentosidine serum levels. The levels of pentosidine in serum are higher than in synovial fluid. Thereby, we suggest that systemic circulation represent the main source of pentosidine production that is probably the result of chronic course of the inflammatory disease, however, it is not related to acute inflammatory response or disease activity.

Comparing the serum and synovial fluid pentosidine levels in RA patients with those levels previously reported by our group in OA patients, we found, unlike the others (Chen et al 1999, Chen et al 1998, Takahashi et al 1997), that there is only insignificant increase of body fluid pentosidine in RA patients. Since the mean age of the OA group was significantly higher, age-related increase of pentosidine might be the reason for this increase in OA patients. Previously, it has been shown that AGE can modify IgG and induce persistent IgM anti-IgG-AGE antibody response and thus can play a role in immune response in RA (Newkirk et al 2003, Lucey et al 2000). Hein et al. (Hein et al 2004) demonstrated association between serum pentosidine and pro-inflammatory cytokine IL-6 in patients with RA. Moreover, they found higher synovial fluid pentosidine in rheumatoid factor positive patients than in those with negative rheumatoid factor. In this consequence we explored a putative association between pentosidine and anti-CCP antibodies – a specific marker for the diagnosis and prognosis of RA. Despite the fact that anti-CCP positive patients tended to have higher serum levels of pentosidine, the difference between anti-CCP positive and anti-CCP negative patients with respect to pentosidne levels was not statistically significant. According to our results, there is no clear association between pentosidine levels and anti-CCP antibodies as a marker of immune response.

In conclusion, our study does not support the idea that pentosidine represents a valuable marker of disease activity in patients with RA. Moreover, any relationship between pentosidine and markers of cartilage breakdown or immune response was not demonstrated. However, it has been recently shown that advanced glycation end products can modulate behavior of synovial fibroblasts and chondrocytes, activate MAP kinase erk and NF-kappaB, and to stimulate
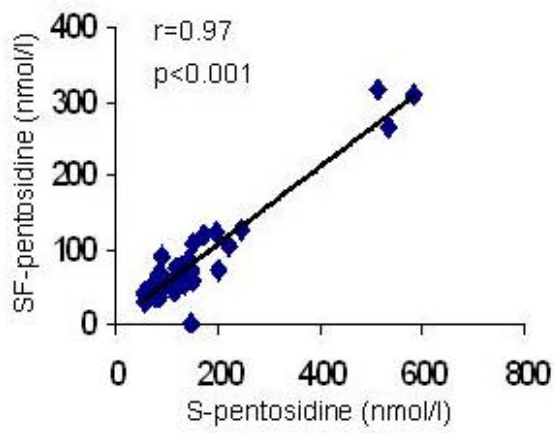
production of some MMPs (Loeser et al 2005, Steenvoorden et al 2006). Thus, advanced glycation could contribute to the joint destruction during chronic rheumatic diseases in situ, which uncover new paradigm for the future research.

Fig.1 The levels of pentosidine in serum correlated significantly with that in synovial fluid in patients with rheumatoid arthritis.

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TABLES

Table 1 Characteristics of the patients with rheumatoid arthritis (RA) and control individuals.

Characteristics	RA (n=39)	Controls (n=38)	p
Age (years)	52.8±2.3	58.9±1.6	NS
Sex (male/female)	7/32	15/23	-
Disease duration (years)	9.6±1.1	-	-
DAS28 score	5.6±0.2	-	-
HAQ	1.2±0.1	-	-
Serum			
Pentosidine (nmol/l)	155.0±20.9	97.7±4.0	0.03
CRP (ng/ml)	41.8 ±6.1	-	-
ESR (1st hour)	38.1±4.1	-	-
COMP (ug/ml)	3.5±0.1	3.3±0.2	NS
Anti-CCP (positive/negative)	38/62%	0/100%	<0.001
Synovial fluid			
Pentosidine (nmol/l)	85.4±11.3	-	-
Leukocyte count	6865.8±1083.9	-	-
COMP (ug/ml)	23.8±2.5	-	-

DAS, disease activity score; HAQ, health assessment questionnaire; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; COMP, cartilage oligomeric matrix protein; CCP, cyclic citrullinated peptide.