α_1 -Antitrypsin in serum and synovial fluid in rheumatoid arthritis

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Observations suggest that lysosomal enzymes released from synovial cells or leucocytes may be important in the pathogenesis of the inflammatory process in the joints of patients with rheumatoid arthritis (Weissmann, 1966; Cochrane, 1968). A likely source of these lysosomal enzymes is a synovial fluid polymorphonuclear leucocyte (Hollander, McCarty, Astorga, and Castro-Murillo, 1965) which has been found to engulf rheumatoid factor, immunoglobulins, complement, and other materials (Barnhart, Riddle, and Bluhm, 1967; Malinin, Pekin, Zvaifler, 1967; Brandt, Cathcart, and Cohen, 1968; Vaughan, Barnett, Sobel, and Jacox, 1968). Various protease inhibitors are present in serum, including α_2 -macroglobulin, inter-alpha-trypsin inhibitor, α_2 -antitrypsin, α_1 -antitrypsin, and α_1 -antichymotrypsin (Schwick, Heimbürger, and Haupt, 1966). However, the principal proteolytic enzyme inhibitor in human serum is α_1 -antitrypsin, a glycoprotein that inhibits trypsin (Kueppers, 1971), plasmin (Heimbürger and Haupt, 1966), thrombin (Rimón, Shamash, and Shapiro, 1966), chymotrypsin (Kueppers, 1971), elastase (Janoff, 1972), and proteolytic enzymes from granulocytes (Kueppers and Bearn, 1966). In this study we investigated the role of α_1 -antitrypsin in regulating the joint inflammation of rheumatoid arthritis by measuring its concentration in sera and synovial fluid.

Material and methods

Serum was obtained from forty healthy blood donor controls and from 24 patients with classic and definite rheumatoid arthritis (diagnostic criteria of American Rheumatism Association) (Ropes, Bennett, Cobb, Jacox, and Jessar, 1959). Knee synovial fluid was obtained by needle aspiration from normal volunteers and from patients with degenerative arthritis, classic and definite rheumatoid arthritis, and other forms of joint disease. Both sera and synovial fluid were obtained on the same day from most of these patients.

The concentration of α_1 -antitrypsin in sera and synovial

fluid was determined by the quantitative radial immunodiffusion method of Mancini, Carbonara, and Heremans (1965) by using specific antisera to human α_1 -antitrypsin (Beringwerke). This antisera gave a major band in the α region when analysed by immunoelectrophoresis with normal human serum; two other faint bands also were seen. Serum and synovial fluid α_1 -antitrypsin molecules gave a reaction of identity in Ouchterlony analysis (Ouchterlony, 1958) and had similar sedimentation coefficients on sucrose density gradient ultracentrifugation, so the same standards were used for the serum and synovial fluid measurements. Women taking hormones or oral contraceptives were excluded from this study. Total protein concentrations in synovial fluid were determined by the biuret method (Kabat and Mayer, 1961).

Results

Age and sex had little influence on serum α_1 -antitrypsin levels and were therefore not considered further in this study. α_1 -Antitrypsin levels were significantly elevated in both the serum and the synovial fluid of patients with classic and definite rheumatoid arthritis as compared with normal serum controls and normal and degenerative arthritis synovial fluids (Table). Comparison of α_1 -antitrypsin concentrations of ten patients (eight with rheumatoid arthritis) revealed a positive correlation ($r = 0.84$) between the level in synovial fluid and that in serum (Fig. 1). There was also a positive relationship ($r = 0.79$) between total protein level and α_1 -antitrypsin concentration in individual synovial fluid specimens from patients with various joint diseases (Fig. 2). In two patients with juvenile rheumatoid arthritis, the serum α_1 -antitrypsin concentrations were 525 mg./100 ml. and 495 mg./100 ml. respectively. α_1 -Antitrypsin concentrations (mg./100 ml.) in the synovial fluid of four patients with gout were 136, 141, 159, and 162 mg. and in three patients with systemic lupus erythematosus they were 218, 222, and 246 mg. These concentrations were all higher than the normal controls, which were less than 110 mg.

Table Concentrations of α_1 -antitrypsin in serum and synovial fluid

Source	No. of cases	α_1 -Antitrypsin (mg./100 ml.) Mean	SD
Serum			
Normal controls	40	191	44
Classic and definite RA	24	278*	68
Synovial fluid			
Normal controls	5	78	17
Degenerative arthritis	15	84†	26
Classic and definite RA	21	148‡	46

* Significantly different from controls ($P < 0.001$; t test).
† Significantly different from classic and definite RA ($P < 0.0001$; rank-sum test).
‡ Significantly different from controls ($P < 0.002$; rank-sum test).

FIG. 1 Correlation of α_1 -antitrypsin concentrations in serum and synovial fluid in ten patients.

Solid circles, classic and definite rheumatoid arthritis (8); open circle, possible rheumatoid arthritis (1); cross ($\times$), temporal arteritis (1)

Discussion

α_1 -Antitrypsin is a potent proteolytic enzyme inhibitor, and approximately 90 per cent. of the total inhibitory capacity of serum trypsin can be attributed to it (Kueppers, 1971). Laurell and Eriksson (1963) first described the association between chronic obstructive pulmonary disease beginning at an early age and serum α_1 -antitrypsin deficiency. A lack of α_1 -antitrypsin in patients with rheumatoid arthritis could allow inflammation to increase because of uninhibited lysosomal enzymes. Conversely, higher than normal concentrations of α_1 -antitrypsin could help to control tissue damage by effecting a response of these enzymes. Cleve and Behrend (1966) and Müller and Müller-von Voigt (1968) reported that α_1 -antitrypsin factor increased in serum from patients with rheumatoid arthritis. The absolute values differ from those which we have obtained because of methodological variations. They did not measure α_1 -antitrypsin in the synovial fluid.

FIG. 2 Correlation of synovial fluid α_1 -antitrypsin and total protein concentrations in 38 patients.

Solid circles, classic and definite rheumatoid arthritis (17); solid squares, degenerative arthritis (17); solid triangles, normal joint (4)

The significance of the elevation of α_1 -antitrypsin concentrations in serum and synovial fluid in patients with rheumatoid arthritis could not be determined from our studies. Our data are consistent with the concept that α_1 -antitrypsin may help to regulate joint inflammation by inhibiting lysosomal enzyme attack on the joint tissues. It is commonly observed that rheumatoid arthritis improves during pregnancy and may relapse after delivery. The α_1 -antitrypsin elevation that occurs during pregnancy may possibly be important in this phenomenon. Clearly, the inflammation in rheumatoid arthritis is not related to a lack of α_1 -antitrypsin, at least as measured by this immunological assay.

Summary

To investigate the role of α_1 -antitrypsin in joint inflammation, we measured its concentrations in sera and synovial fluid from patients with rheumatoid arthritis, degenerative arthritis, and other joint diseases, and compared these to normal control levels. There was a significant elevation of α_1 -antitrypsin concentrations in both serum and synovial fluid from patients with rheumatoid arthritis. There was a positive relationship between the α_1 -antitrypsin concentration in serum and that in synovial fluid in individual patients and between the total protein of synovial fluid and the α_1 -antitrypsin concentration in individual specimens. These results indicate that the inflammation in rheumatoid arthritis brings about an increased concentration of α_1 -antitrypsin, presumably in response to the increased release of lysosomal enzymes.

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