patients with a short disease duration is marked by oedema, while the skin of patients with a long disease duration is marked by atrophic changes.

The main advantage of ultrasonography is its objectivity, but the interpretation of the results may be difficult. Still, it may be a useful tool for the evaluation and follow-up of patients with SSc if used in selected skin areas and when reservations are made for the limitations of its use in the description of sclerotic skin.

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Elevated Serum Xylosyltransferase Activity Correlates with a High Level of Hyaluronate in Patients with Systemic Sclerosis

Sir,

Systemic sclerosis (SSc) is a chronic inflammatory disease of the connective tissue characterized by excessive accumulation of extracellular matrix in skin and internal organs. Sclerotic processes lead to a massive deposit of collagen fibrils and to an elevation of proteoglycan metabolism in sclerotic organs (1). In skin biopsies of SSc patients elevated concentrations of chondroitin sulphate and dermatan sulphate were observed, indicating their role in fibrosis (2).

Chondroitin sulphate, dermatan sulphate and heparan sulphate are bound to the proteoglycan core protein by a xylose-galactose-galactose linking region (3). UDP-D-xylose:proteoglycan core protein (β-D-xylosyltransferase (EC 2.4.2.26, XT) is the chain-initiating enzyme involved in the biosynthesis of proteoglycans. The enzyme catalyses the transfer of D-xylose from UDP-D-xylose to specific serine residues of the core protein and was shown to be secreted simultaneously into the extracellular space with chondroitin sulphate proteoglycans (4). These proteoglycans are bound to hyaluronate chains and collagen fibrils in connective tissue. Thus, it is suspected that fibrotic alterations of the connective tissue and the increased biosynthesis of chondroitin sulphate proteoglycans in sclerotic processes result in elevated levels of XT and hyaluronate in the circulation.

MATERIAL AND METHODS

Serum specimens were collected from 16 female and 4 male patients suffering from SSc. All patients fulfilled the American College of Rheumatology criteria for the classification of SSc (5). The classification of SSc in the 2 subtypes (limited and diffuse disease) was done according to LeRoy et al. (6). Four patients, age range 32–57 years, were suffering from the diffuse form of SSc and the remaining ones, age range 24–82 years, from limited SSc. In all patients studied the skin was affected by sclerotic lesions. Furthermore, the internal organ systems of 11 patients were affected by sclerotic processes. The determination of XT activity using recombinant bikunin as acceptor was performed as described previously (7). Hyaluronic acid (HA) in serum samples was determined by a radiometric HA test (Pharmacia AB, Uppsala, Sweden) and alanine aminotransferase (ALT) activity was measured with a mechanized analyser (Dimension RxL, Dade-Behring, Munich, Germany). Statistical analysis was performed using *t*-test, correlation and regression analysis using Pearson's correlation coefficient and analysis of variance (ANOVA) including F-test. p values of 0.05 or less were considered significant.

RESULTS AND DISCUSSION

We investigated XT activities in blood specimens from 16 female patients with systemic sclerosis and in serum samples from blood donors ($n=315$). As analysis of XT activities in blood donors revealed an age and sex dependence (7), the control groups in our experiments were of same age and sex as the SSc patients. Since only 4 male patients were available

for analysis, they were excluded. XT activities in women with SSc (age range 24–72 years) were significantly elevated compared with female blood donors ($n=165$, age range 20–65 years). Thus, in serum specimens of women with SSc, the mean XT activity was 1.5 fold higher (mean value 1.25 mU/l, SD 0.21) than in female blood donors of corresponding age (mean value 0.83 mU/l, SD 0.17).

Elevated concentrations of dermatan sulphate and chondroitin sulphate proteoglycans have been observed in skin biopsies from scleroderma patients (2). Biosynthesis of these glycosaminoglycans is initiated by XT, which is secreted into extracellular space together with chondroitin sulphate proteoglycans (4). Therefore, we suggest that the observed elevation of XT activity in blood is a consequence of the increased proteoglycan biosynthesis and secretion into the fibrotic skin and organ systems. These results are in accordance with previous findings of elevated blood XT activities in patients suffering from lung fibrosis and hepatitis C virus induced liver fibrosis (unpublished observations).

We also determined the circulating hyaluronate (HA) levels in blood specimens from SSc patients. HA levels were found to be increased in liver diseases and in rheumatoid arthritis (8). In order to exclude an elevation of HA plasma levels due to a liver disease in the SSc patients investigated we measured the alanine aminotransferase (ALT) activity. ALT activity is a diagnostic marker suitable for the determination of liver disorders. In all specimens the ALT activity was found to be lower than 20 U/l, indicating that the liver was not affected in any of the SSc patients investigated.

Serum hyaluronate levels in SSc patients (66 μg/l; SD 28.1) were slightly elevated compared with 20 healthy controls of corresponding sex and age (45 μg/l; SD 15.4). These results are in accordance with Freitas et al. and Hørslev-Petersen et al., who found significantly increased levels of plasma hyaluronate in SSc patients (mean values 55 μg/l and 63 μg/l, respectively) with a comparable HA assay (9,10). However, a previous study from Engström-Laurent et al. has shown higher hyaluronate levels in the serum of SSc patients (mean value 131 μg/l, SD 67.0) (11). Serum HA concentration was found to be higher in patients with progressive disease than in patients without rapid progression (11). The majority of the patients investigated in our study were suffering from the limited form of systemic sclerosis, which is characterized by a mild progression of the disease. Thus only slightly elevated HA concentrations were observed. Furthermore, we found a significant positive correlation of HA concentration and XT activity in blood (correlation coefficient $r=0.53$, $p<0.01$). Elevated levels of serum HA in scleroderma patients were assumed to result from an enhanced synthesis by abnormally activated fibroblasts in inflammatory processes (9).

In our study the determination of the hyaluronate concentration just failed to show a significant elevation of plasma HA in female SSc patients. However, the significant correlation of circulating hyaluronate and serum XT activity allows us to conclude that the elevated XT activity observed in SSc patients is a direct consequence of the fibrotic process in sclerotic organ systems. Excessive accumulation of connective tissue is considered to be responsible for the main clinical symptoms in systemic sclerosis. Therefore, in addition to the aminoterminal type III procollagen peptide concentration (10) serum XT activity is proposed to be a marker for determination of disease activity in systemic sclerosis due to its direct linkage to proteoglycan and connective tissue metabolism.

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