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Ultrasonic Measurement of Skin Thickness in Patients with Systemic Sclerosis

Sir,

Clinical evaluation of the thickness, texture and fixation of the skin, and the extent of dermal changes is necessary for the estimation of the progression and remission of systemic sclerosis (SSc) (1). Such observations may carry important prognostic information (2, 3). Measuring skin thickness by means of high-frequency ultrasound may represent a useful objective and non-invasive method (4), the results of which seems to correlate with clinical and radiographic evaluations (5, 6). Several ultrasound studies showed clinically involved skin of patients with SSc to be thicker than the skin of normal persons (6–9).

We have studied 20 Danish Caucasian female outpatients with SSc according to the classification criteria of the American College of Rheumatology (10) and 20 healthy age-matched women by means of ultrasound determination of skin thickness and clinical skin scoring. The patients had a mean age of 67.6 years (range 43–83 years) and a mean disease duration of 17.5 years (range 4–36 years). The disease activity and the medication (including or exclusive of penicillamine) of the patients was stable. Four patients had diffuse SSc and the remainder had limited SSc.

Ultrasonography was performed by means of a 20 MHz ultrasound scanner (Dermascan, Cortex Technology, Hadsund, Denmark). Combined A- and B-mode scanning was used to measure the skin thickness, which was defined as the distance between the dermal-epidermal junction and the dermal-subcutaneous interphase. Measurements were performed 3 times by 3 different observers, the result being the mean of these 9 measurements. All measurements were performed in the afternoon in 5 sites:

- region 1: mid portion of the right dorsal 3rd proximal phalanx;
- region 2: dorsal area between 2nd and 3rd right metacarpophalangeal joint;
- region 3: the dorsal aspect of the right forearm, 2 cm above the wrist;
- region 4: the middle of the dorsal aspect of the right forearm;
- region 5: the area of the manubrium of the sternum.

Two experienced observers estimated the skin scores of the 5 regions mentioned using a modified Rodnan score (6): score 0: normal skin; 1: thickened skin; 2: thickened skin which could not be pinched; 3: thickened and immobile skin.

The mean result of the 2 observers was the final skin score, which was compared with the other measurements.

The skin of the digital regions of the SSc patients was significantly thicker than that of the controls. In the 5 regions the values obtained in patients and controls were, respectively (mean $\pm$ +SD), 1.49 ± 0.34 mm vs. 1.22 ± 0.31 mm ($p < 0.001$), 1.25 ± 0.32 mm vs. 1.00 ± 0.19 mm ($p < 0.001$), 1.20 ± 0.37 mm vs. 1.08 ± 0.22 mm ($p > 0.05$), 1.09 ± 0.35 mm vs. 1.06 ± 0.26 mm ($p > 0.05$), and 1.07 ± 0.27 mm vs. 1.11 ± 0.26 mm ($p > 0.05$). In the patients the skin thickness increased with an increasingly distal location of the regions studied. The skin of the fingers of the controls was also thicker than that of the other regions measured, but the trend of progressive thickening of the skin with an increasingly distal location of the regions studied was not found in the controls. ANOVA was performed in order to identify the contributions to the variation of the skin thickness caused by the skin regions and by the skin scores. The contribution of the regions was significant ($p = 0.03$), but not of the skin scores ($p = 0.68$). Hence, the significant overall correlation found between skin thickness and skin scores (rho $= 0.36$, $p < 0.001$) was explained by inherent properties of the regions, unrelated to the skin scores. A significant relationship between the skin thickness and the skin scores was found only for the proximal phalanx region (rho $= 0.56$, $p = 0.01$). An inverse relationship between the skin thickness and the disease duration was found in the proximal phalanx region (rho $= -0.49$, $p = 0.03$), but not in the other regions studied. The skin thickness was unrelated to the age of the patients and the controls.

The present study shows poor correlation between the skin thickness estimated by ultrasonography and the skin score in most of the skin regions examined, probably because the 2 methods measure different properties of the skin. The skin score is dependent, not only on the thickness of the skin, but also on its texture and its fixation, while, in this study, the ultrasonography merely measured the thickness of the skin. The present study confirms previous findings of increased thickness of involved skin of the patients with SSc (6–9). However, the thickness of clinically uninvolved skin was not increased, contrary to the findings in a previous Japanese study (9). The skin of our Danish controls was sonographically thicker than the skin of the Japanese controls, the differences being significant for the forearm and for the area between the knuckles. In the Danish controls the skin of the fingers was thicker than the skin of the other regions studied, the opposite being true for the Japanese controls. The skin thickness of the Danish controls was similar to that found in other studies of Caucasian control persons (5, 6). These findings indicate that skin thickness may vary with ethnic background. The inverse correlation between skin thickness and disease duration is explained by the wide variation in the disease duration in the present, as well as in the Swedish study (6), because the skin of

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