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Renal Hemodynamic Characteristics and Their Correlation with Serum Autoantibodies in Patients with Systemic Sclerosis

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Summary. Purpose. **To clarify the characteristics of renal hemodynamics and their correlation with serum autoantibodies in patients with systemic sclerosis (SSc).**
Methods: **Glomerular filtration rate (GFR) and renal plasma flow (RPF) were analyzed retrospectively in three groups totaling 50 Japanese patients with SSc treated between 1982 and 1998. The filtration fraction (FF) was calculated from the values obtained for GFR and RPF (GFR/RPF). The presence of antibodies to DNA topoisomerase 1 (A-Topo) and centromere (ACA) were also examined in relation to renal hemodynamics.**
Results: **The GFR was abnormally low in 8 (16.0%) patients, but a decreased RPF was observed in 21 (42.0%). Thus, an increased FF was frequently observed (29/50; 58.0%). A-Topo was detected in 23 patients (group A) and ACA in 10 (group B). In the remaining 17 patients (group C), however, these autoantibodies were not detected. Diffuse scleroderma or pulmonary fibrosis was more prevalent in group A than in group B. The mean GFR in group B was significantly lower than that in group C. The mean RPF in group B was significantly lower than that in the other 2 groups. Patients with an increased FF were more often found in group B than in the other 2 groups.**
Conclusions: **A reduction in RPF disproportionate to the reduction in GFR, as demonstrated by the high FF, was observed frequently in SSc patients. Although ACA was associated with less serious cutaneous or pulmonary involvement, renal hemodynamic alterations seemed to correlate with the presence of ACA.**

Key words—systemic sclerosis, renal hemodynamics, anti-DNA topoisomerase 1 antibody, anti-centromere antibody, renal plasma flow, filtration fraction.

INTRODUCTION

Systemic sclerosis (SSc) is characterized pathologically by an excessive accumulation of various collagens in the involved organs.[1] Although skin sclerosis is a primary clinical feature, multisystem disorders such as pulmonary fibrosis, renal disorder, and gastrointestinal dysfunction are often concomitant with SSc.[2] Several authors have reported increased mortality due to restrictive pulmonary disease in SSc patients.[3,4] On the other hand, renal disorders remain the cause of death in 10 to 20% of SSc patients.[4] Therefore, basal renal hemodynamics merits further investigation in SSc patients. Recently, several autoantibodies such as anti-DNA topoisomerase 1 (A-Topo) and anti-centromere antibody (ACA) have been measured for the evaluation of organ involvement in SSc patients. It has been clearly shown that A-Topo and ACA are not only specific for SSc but might be useful for the identification of disease subsets.[5] However, there have been very few attempts to examine the relation between renal hemodynamics and immunologic abnormalities in relatively large series of patients with SSc. We investigated the renal hemodynamics of Japanese SSc patients, most of whom showed no clinical renal disorder. The present retrospective study was undertaken to examine the relation between renal hemodynamics and autoantibodies, in particular, serum A-Topo and ACA in these patients.

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PATIENTS AND METHODS

Patients

This series included all patients hospitalized with SSc who underwent renal hemodynamic evaluation at Niigata University Hospital between 1982 and 1998. All patients satisfied the 1980 criteria of the American College of Rheumatology (formerly the American Rheumatism Association) for SSc.[6] Patients with insufficient clinical or immunologic data or who were taking nonsteroidal anti-inflammatory drugs were excluded from this analysis. Fifty patients met the criteria: 11 men and 39 women whose mean (±SD) age at the time of evaluation was 52.2 (±13.0) years (range, 14 to 77 years). The mean (±SD) duration of SSc (from the onset of Raynaud's phenomenon to the time of evaluation) was 6.0 (±5.6) years (range, 3 months to 22 years). No patient was treated with acetylsalicylic acid or methotrexate throughout their clinical course.

Patients were classified as having diffuse cutaneous or limited cutaneous disease according to published recommendations.[7] Specifically, diffuse scleroderma was diagnosed in patients who had skin indurations involving the face, extremities, and trunk. Limited scleroderma was diagnosed in patients who had skin changes confined to the hands, face, feet, and forearms. On initial evaluation, patients underwent routine chest roentgenography and computed tomography. A patient was considered to have hypertension if the systolic pressure was over 160 mmHg, the diastolic pressure was over 90 mmHg, or the patient was receiving antihypertensive drug therapy regardless of blood pressure. Clinical laboratory tests were performed using standard hospital laboratory procedures.

Renal function and urinary examination

Glomerular filtration rate (GFR) and renal plasma flow (RPF) were measured simultaneously by a standard clearance technique[8] using sodium thiosulphate and sodium para-aminohippurate, respectively, after obtaining each patient's informed consent. All clearance data were corrected for standard body surface area (1.73m^2). The filtration fraction (FF) was calculated from the actual values obtained for GFR and RPF (GFR/RPF). In our hospital, the normal GFR is considered to range from 96.9 to 165.0 ml/min in men and from 76.8 to 156.8 ml/min in women. The normal RPF range is considered to be between 466.2 to 747.3 ml/min in men and between 450.6 to 711.0 ml/min in women. The normal FF is approximately 20%. An increased FF level was defined in this study as 23% or more. Renal function was also determined based on serum creatinine. For descriptive purposes, loss of renal function was assumed when the serum creatinine level exceeded 1.1 mg/dl in men or 0.8 mg/dl in women. Hematuria was defined as five or more red blood cells per high power field on urinalysis, and proteinuria was defined as 0.3 g/day or more.

Laboratory and immunologic analyses

Indirect immunofluorescence on commercially prepared HEp-2 cells was used for the determination of ACA. The presence of ACA was identified by the characteristic discrete-speckled pattern. Furthermore, A-Topo was assayed by double immune diffusion using extractable nuclear antigens with DNA-topoisomerase 1 antigenic activity. Antigens were prepared from calf thymus obtained from MBL Co., Ltd (Nagoya, Japan).[9] Serum samples were collected at the time of hospital admission and stored at −70℃ until use.

Statistics

To calculate the statistical significance of differences, Student's *t*-test, Wilcoxon's test, Fisher's exact test, and chi-square analysis were used. P values less than 0.05 were considered significant.

RESULTS

Of the 50 SSc patients, 11 had clinical renal disorders at the time of admission: 8 with proteinuria and/or hematuria and 3 with hypertension. Diffuse cutaneous lesions were observed in 20 patients, and limited cutaneous SSc was discerned in 30 patients. The incidence of pulmonary fibrosis was 68% of all cases (34/50). Increased serum creatinine was observed in only 2 patients. Mean (±SD) GFR and RPF values for the entire group were 117.4 (±37.0) ml/min and 508.8 (±202.8) ml/min, respectively. A highly significant correlation was observed between the GFR and RPF ($r=0.87$, $p<0.001$). The figure shows renal hemodynamic status at the time of evaluation. The GFR was abnormally low in only 8 (16%) patients and was within the normal range in 33. In contrast, abnormally low RPF values were noted in over 40% of patients. In 13 patients, the RPF was abnormally low but was not accompanied by a decrease in GFR. Therefore, the functional status of RPF differed from that of GFR. The increased FF was frequently (29/50; 58.0%) observed irrespective

Table 1. Clinical characteristics in the three subgroups defined according to the positivity of autoantibodies

	Group A (n=23)	Group B (n=10)	Group C (n=17)
Age (years)#	50.5(14.0)	58.4(13.8)	51.0(10.3)
Duration of SSc (months)#	60(66)	117(80)	62(51)
Sex (male/female)	4/19	1/9	6/11
Scleroderma (diffuse/limited)	12/11	1/9*	7/10
Pulmonary fibrosis, n (%)	20(87)	3(30)*	11(65)

* $p<0.05$ vs Group A

Data are shown as mean (SD).

Table 2. Renal function in the three subgroups defined according to the positivity of autoantibodies

	Group A (n=23)	Group B (n=10)	Group C (n=17)
GFR (ml/min)#	115.0(35.1)	93.1(36.4)***	135.1(33.0)
RPF (ml/min)#	511.1(192.6)	345.9(102.5)*,***	601.6(207.9)
FF (%)#	23.3(3.7)	26.7(5.5)	24.1(7.4)
FF ≧ 23%, n (%)	12(52)	9(90)*,**	8(47)

* $p<0.05$ vs Group A, ** $p<0.05$ vs Group C, *** $p<0.01$ vs Group C

Data are shown as mean (SD).

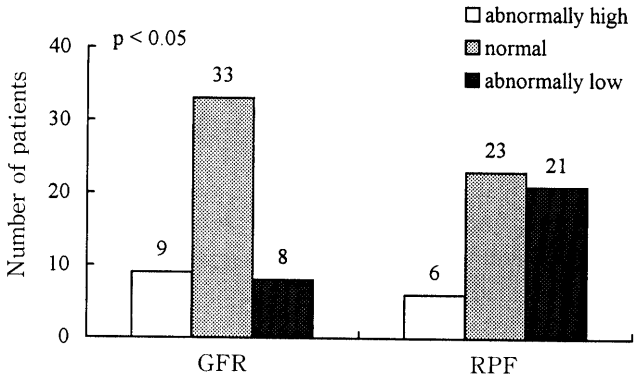

Fig. 1. Renal hemodynamic status at the time of evaluation.

of the GFR. The mean (±SD) FF of the 50 SSc patients was 24.3 (±5.6) %. Mean FF levels were comparable between the patients with clinical renal disorders (n=11, 23.2%) and those without clinical renal disorders (n=39, 24.6%).

The patients were classified into three subgroups according to their autoantibody status: (A) patients with A-Topo (n=23), (B) patients with ACA (n=10), and (C) patients without these autoantibodies (n=17). Clinical characteristics of patients in the three groups are summarized in Table 1. Mean age and mean duration of SSc at the time of evaluation were comparable between the three groups. Sex ratios were also similar between the three groups. Diffuse scleroderma was more prevalent in group A patients than in group B patients. Furthermore, the incidence of pulmonary fibrosis was much higher in group A patients than in group B patients. The frequency of diffuse cutaneous lesions or pulmonary involvement in group C patients was almost midway between the high frequency found among group A patients and the relatively low frequency found among group B patients. Renal hemodynamics in these three subgroups are shown in Table 2. The mean GFR in group B patients was lower than that in group C patients. Furthermore, the mean RPF in group B patients was significantly lower than that in the other two groups. The mean FF was higher in group B patients than that in the other two groups, but these differences were not statistically significant. An increased FF was more prevalent in group B than in the other two groups.

DISCUSSION

In this study, a relatively decreased RPF was recognized frequently in SSc patients. These results are, in part, consistent with a previous observation by Clements et al.[10] who noted isolated decreases in RPF in SSc patients. In the present study, clinical renal disease was observed in only 11 of 50 SSc patients. Therefore, SSc itself may be responsible for these hemodynamic changes. We also found that measuring only serum creatinine or GFR might lead to underestimating the exact frequency of renal hemodynamic alterations in SSc patients. Therefore, relative evaluations of GFR and RPF, namely the determination of FF, may be clinically useful for determining the renal hemodynamic characteristics of SSc patients. In the present study, GFR was measured by a relatively conventional method.[8] Inulin clearance has been regarded as the most accurate method of measuring GFR.[11] However, GFR values determined by sodium thiosulphate clearance are thought to correlate well with those ascertained by inulin clearance.[12] At any rate, GFR and RPF should be determined simultaneously in SSc patients.

Immunologic abnormalities connect closely to various clinical aspects of SSc. Cutaneous and pulmonary involvements are believed to correlate with A-Topo.[5] Furthermore, ACA has been associated with less serious involvements of skin or lung.[5] The present study has confirmed these findings. Recently, the presence of an antibody to RNA polymerase has been associated with a high prevalence of serious renal involvement in SSc patients.[13,14] However, there have been few studies undertaken to clarify the correlation between autoantibodies and renal hemodynamic alterations in SSc patients, including those with subclinical renal disorders. The present immunologic analysis showed renal hemodynamic parameters to be related to the presence of ACA. Furthermore, A-Topo showed only a low correlation with renal hemodynamic characteristics in SSc patients.

A positive correlation between limited SSc and peripheral vascular disorders was suggested in a recent study.[15] Furthermore, pulmonary hypertention without pulmonary fibrosis reportedly is more frequent in limited SSc than in diffuse SSc.[16] Stupi et al. reported that, according to immunologic evaluation, ACA was present frequently in SSc patients with isolated pulmonary hypertension.[17] Therefore, SSc patients with ACA, almost always accompanied by limited cutaneous lesions, may be more likely to develop vascular disorders such as renal hemodynamic alterations. In conclusion, certain characteristic renal hemodynamic changes are found in SSc patients regardless of the status of their renal glomerular function. ACA correlated significantly with renal hemodynamic abnormalities. Since several factors may reflect renal hemodynamics in cases of SSc, further study is necessary to understand better the contribution of autoantibodies to renal hemodynamic characteristics in SSc patients.

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