Renal haemodynamic characteristics in patients with lupus nephritis

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Abstract

Objective—To clarify the characteristics of renal haemodynamics in patients with lupus nephritis (LN).

Methods—The glomerular filtration rate (GFR) and renal plasma flow (RPF) of 37 patients with active LN were studied longitudinally over an interval of 8 to 144 weeks during treatment with corticosteroids or cytotoxic drugs, or both. All patients had clinical renal disorders and underwent renal biopsies.

Results—Analysis of renal biopsy specimens showed that 31 patients had class IV LN. Class II, III, and V LN were present in two patients each. The average GFR increased significantly from 65.4 (SD 33.0) in the pretreatment stage to 86.6 (31.6) ml/min in the post-treatment stage, accompanied by an improvement in urinary or immunological abnormalities, or both. On the other hand, RPF decreased significantly from 625.2 (243.0) to 519.8 (179.0) ml/min. Therefore, the filtration fraction (FF) increased significantly from 10.7 (4.3)% to 16.8 (3.7)%. Low FF was recognised predominantly in patients with class IV LN, but was also observed in patients with other classes. The FF returned towards normal irrespective of the degree of GFR recovery. No significant changes were observed in the levels of blood pressure.

Conclusion—A reduction in GFR out of proportion to the reduction in RPF as demonstrated by the low FF values was related to the severity of LN or disease activity, or both. Therefore, relative evaluation of GFR and RPF, namely the determination of FF, may be a useful clinical parameter to determine the status of LN.

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As a result of immunological abnormalities, renal disorders occur frequently in patients with systemic lupus erythematosus (SLE).[1–3] The prognosis of patients with SLE is determined by the severity of renal involvement.[4–7] Thus, evaluation of both histological abnormalities and renal function is important in SLE patients. Many studies concerning the histological evaluation of lupus nephritis (LN) have been reported.[8–11] However, reports on the evaluation of renal haemodynamics in LN give conflicting results.[12–14] This longitudinal study was performed to evaluate the clinical significance of measurements of glomerular filtration rate (GFR) and renal plasma flow (RPF) in patients with active LN during treatment with high dose corticosteroids or cytotoxic drugs, or both. The findings obtained in this study mostly represent those of patients with diffuse proliferative LN.

Methods

PATIENTS

This series comprised all hospitalised patients with SLE who underwent serial haemodynamic examinations during both the active and inactive phases of LN in Niigata University Hospital between 1982 to 1996. Patients whose history was complicated by uncontrolled hypertension, congestive heart failure, severe liver disease, or uncontrolled diabetes mellitus were excluded. Patients with insufficient clinical data, or no clinical renal disorder were also excluded. Finally, 37 patients, one male and 36 females, with a mean (SD) age at admission of 33.7 (13.8) years (range 15 to 65 years), were analysed. The mean (SD) duration of disease before admission was 70.9 (68.9) months (range 1 to 300 months). All patients satisfied the 1982 revised criteria of the American College of Rheumatology (ACR; formerly, American Rheumatism Association) for SLE.[15] All patients had definite evidence of active disease, including clinical renal disorders (proteinuria, haematuria, or renal dysfunction) and immunological abnormalities such as hypocomplementaemia or high anti-DNA antibody levels, or both. Thus, all patients were treated with at least 40 mg/day of prednisolone initially. The corticosteroid dose was then tapered upon improvement of the patient's condition as indicated by urinary or immunological parameters, or both. Cytotoxic drugs were used during these studies in 21 patients with insufficient improvement by initial corticosteroid therapy. Oral cyclophosphamide was used in 16 patients and mizoribine in five.

RENAL FUNCTION AND URINARY EXAMINATION

GFR and RPF were simultaneously measured with an indwelling catheter in the urinary bladder by standard clearance techniques using sodium thiosulphate and sodium paraaminohippurate,[14 16 17] respectively, after obtaining each patient's informed consent. Inulin could not be used in this study, because it is not allowed as laboratory reagent in Japan at the present time. All clearance data were corrected to standard body surface area (1.73 m^2). The filtration fraction (FF) was calculated from the actual values obtained for GFR and RPF (GFR/RPF). Repeat clearance

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studies were undertaken on two occasions during the active and inactive phases of LN at least eight weeks apart. The normal GFR in our hospital ranges from 96.6 to 165.0 ml/min in men and from 76.8 to 156.8 ml/min in women. The normal range of RPF is from 466.2 to 747.3 ml/min in men and from 450.6 to 711.0 ml/min in women. The normal value of FF is approximately 20% in our hospital. In the study by Ter Borg *et al*, the normal range of FF is from 18 to 28%.[18] Haematuria was defined as five or more red blood cells per high power field on urine analysis, and proteinuria was defined as urinary protein excretion ≥0.5 g/24 h. Loss of renal function was defined as a concentration of serum creatinine greater than 1.1 mg/dl in men or 0.8 mg/dl in women.

RENAL HISTOLOGICAL EXAMINATION
All patients underwent renal biopsies because of urinary abnormalities or renal dysfunction, or both. Histological evaluations were done by light, electron, and immunofluorescence microscopy.[17 19] Light microscopic evaluation

was performed after staining with haematoxylin and eosin, periodic acid Schiff, periodic acid methenamine silver (PAM), PAM Masson, elastica Masson, and alkaline Congo red. Characteristics of the examined tissue were defined according to the World Health Organisation (WHO) classification,[20] as no glomerular changes (class I), mesangial (class II), focal proliferative (class III), diffuse proliferative (class IV), and diffuse membranous (class V) glomerulonephritis. Immunofluorescence study was performed on cryostat sections using fluorescein isothiocyanate conjugated antiserum samples to human immunoglobulins (IgG, IgA, and IgM), complements (C3, C4, and Clq), and fibrinogen. Electron microscopy was performed with standard procedures as previously reported.[17]

DRUG HISTORY AND BLOOD PRESSURE
The diuretics and antihypertensive drugs used during the interval of observation were surveyed from hospital charts. The patient was considered to have hypertension if the systolic pressure was over 160 mm Hg, or the diastolic pressure was over 90 mm Hg, or the patient was receiving antihypertensive drug treatment regardless of the blood pressure. At the initial haemodynamic examination, nine patients were receiving antihypertensive drugs. Calcium channel blocker was used in six patients, and angiotensin converting enzyme (ACE) inhibitor in two. On the follow up clearance study, 13 patients were receiving antihypertensive drugs. Calcium channel blocker was used in nine patients, and ACE inhibitor in one. Diuretics were used in 13 patients at the initial evaluation, and in 11 at subsequent evaluation. No patients were taking non-steroidal anti-inflammatory drugs.

STATISTICS
For analysis, the following variables were evaluated: age at admission, duration of SLE, urine analysis findings, serum creatinine anti-DNA antibody, total haemolytic complement activity (CH50), serum albumin, and blood pressure. To calculate the statistical significance of differences, Student's *t* test, Fisher's exact test, and χ^2 analysis were used. Variables not normally distributed such as anti-DNA antibody were analysed with Wilcoxon's test. Values of p<0.05 were considered significant.

Table 1   Summary of serial measurements of clinical parameters of 37 SLE patients

Parameters	Pretreatment	Post-treatment	p Value
Proteinuria (g/24 h)	4.1 (2.6)	1.5 (1.2)	<0.01
Serum albumin (g/dl)	2.9 (0.9)	3.4 (0.4)	<0.01
Anti-DNA antibody (U/ml)★	242 (346)	10 (10)	<0.01
CH50 (U/ml)	16.1 (7.6)	36.8 (9.7)	<0.01
Systolic BP (mm Hg)	132 (21)	127 (14)	NS
Diastolic BP (mm Hg)	78 (12)	79 (11)	NS

Values are mean (SD). CH50=total haemolytic complement activity; BP=blood pressure; NS=not significant. ★Anti-DNA antibody was compared in 34 patients.

Table 2   Summary of serial measurements of renal haemodynamic parameters of 37 SLE patients

Parameters	Pretreatment	Post-treatment	p Value
Serum creatinine (mg/dl)	1.04 (0.60)	0.77 (0.25)	<0.01
GFR (ml/min)	65.4 (33.0)	86.6 (31.6)	<0.01
RPF (ml/min)	625.2 (243.0)	519.8 (179.0)	<0.01
FF (%)	10.7 (4.3)	16.8 (3.6)	<0.01

Values are mean (SD). GFR=glomerular filtration rate; RPF=renal plasma flow; FF=filtration fraction.

Table 3   Renal haemodynamic status at the pre- and post-treatment stage of 37 SLE patients

	Abnormally low	Normal	Abnormally high	p Value★
Pretreatment stage				
GFR	25 (68)	12 (32)	0 (0)	<0.01
RPF	9 (24)	14 (38)	14 (38)	
Post-treatment stage				
GFR	15 (41)	22 (59)	0 (0)	<0.05
RPF	15 (41)	16 (43)	6 (16)	

Values are number of patients (%). ★Comparisons between GFR and RPF by χ^2 analysis. Abbreviations as table 2.

Table 4   Renal haemodynamics in SLE patients classified by WHO criteria of lupus nephritis

	Class II (n=2)	Class III (n=2)	Class IV (n=31)	Class V (n=2)
GFR (ml/min)				
Pretreatment	91.8 (22.2)	51.2 (44.2)	60.7 (30.4)	126.7 (1.3)
Post-treatment	117.1 (21.3)	41.8 (41.5)	85.4 (29.3)	118.9 (5.5)
RPF (ml/min)				
Pretreatment	624.3 (91.4)	370.6 (215.4)	609.5 (239.1)	887.9 (20.0)
Post-treatment	604.0 (84.0)	243.5 (229.0)	518.0 (165.2)	741.4 (97.0)
FF (%)				
Pretreatment	15.1 (5.7)	12.4 (4.7)	10.2 (4.3)	14.3 (0.5)
Post-treatment	19.9 (6.3)	16.4 (1.6)	16.7 (3.7)	16.2 (1.3)

Values are mean (SD). Abbreviations as table 2.

Results
The presenting clinical feature was renal disorder in 34 patients, and cutaneous manifestation, pulmonary involvement, and joint involvement each in one patient. Proteinuria was recognised in 36 patients, haematuria in 29, and renal dysfunction in 18 at the time of admission. The mean prednisolone dose at the time of initial haemodynamic evaluation was 55 mg/day. Serial renal haemodynamics were evaluated during an interval of eight to 144 weeks (average, 27.6 weeks). Table 1 shows the serial measurements of clinical parameters. Daily urinary protein excretion decreased significantly. Mean serum albumin concentration increased by 0.5 g/dl. Immunological

Table 5 Serial measurements of urinary, immunological, and renal haemodynamic parameters of two groups according to the improvement of GFR

	Group 1 (n=14)			Group 2 (n=17)		
	Pretreatment	Post-treatment	p Value	Pretreatment	Post-treatment	p Value
Proteinuria (g/24h)	4.0 (2.4)	1.3 (1.0)	<0.01	4.5 (2.9)	1.6 (1.4)	<0.01
Anti-DNA (U/ml)*	235 (318)	10 (8)	<0.01	202 (307)	7 (5)	<0.01
CH50 (U/ml)	15.5 (5.9)	37.8 (7.5)	<0.01	15.8 (8.3)	37.6 (11.2)	<0.01
GFR (ml/min)	57.3 (22.0)	61.4 (20.2)	NS	54.5 (29.1)	99.6 (30.9)	<0.01
RPF (ml/min)	588.5 (223.9)	400.8 (141.3)	<0.01	549.7 (216.6)	560.7 (170.6)	NS
FF (%)	10.0 (2.9)	15.6 (2.8)	<0.01	10.7 (5.7)	18.2 (4.4)	<0.01

Values are mean (SD). Anti-DNA=anti-DNA antibody; CH50=total haemolytic complement activity. Other abbreviations as table 2. *Anti-DNA antibody was analysed in 13 patients in group 1, and 15 patients in group 2.

abnormalities improved significantly during the serial studies. No significant changes were observed in the levels of systolic or diastolic blood pressure.

Table 2 shows the serial measurements of renal haemodynamic parameters. Mean serum creatinine decreased 0.27 mg/dl during these studies. The average GFR increased significantly. On the other hand, RPF decreased significantly. The mean increase in GFR was 32%, or 21.2 ml/min, while RPF fell 17%, or 105.4 ml/min. Thus, FF increased significantly from 10.7 (4.3)% to 16.8 (3.6)%. FF returned to or approached normal values in most of the patients. The mean increase in FF was comparable between 16 patients treated with corticosteroid only (4.9%) and 21 patients treated with cytotoxic drugs (7.0%). Table 3 shows the renal haemodynamic status at the initial and follow up evaluation. At the initial evaluation, the level of GFR was abnormally low in about two thirds of patients. The level of RPF was abnormally low in only nine patients and abnormally high in 14. At the post-treatment stage, the level of GFR was abnormally low in 15 patients, and within normal limits in 22. The number of patients with abnormally high RPF levels decreased from 14 to six. Thus, the functional status of GFR and RPF was significantly different from each other, especially in the pretreatment phase.

Table 4 shows the serial renal haemodynamics in LN patients classified by WHO criteria. Renal biopsy studies before initial corticosteroid therapy showed that 31 patients had class IV LN, and two patients each had class II, III or V LN. The decrease in FF seemed to be more prominent in patients with class IV LN. However, low FF was observed in patients with every other class of LN. The FF returned toward normal irrespective of the WHO classes of LN. The patients were divided into two groups according to the recovery of GFR during these studies: Group 1 patients (n=20) had an improvement in GFR less than 20 ml/min; Group 2 patients (n=17) had an improvement in GFR greater than 20 ml/min. GFR was preserved within normal limits throughout the study in six of the Group 1 patients. Thus, these six patients were excluded from analysis. Table 5 shows a summary of longitudinal changes in clinical parameters and renal haemodynamics in the two groups. Low FF was observed in both groups during the pretreatment phase. Proteinuria and immunological abnormalities improved significantly in both groups. No significant change in the level

of GFR was found in Group 1 patients. The average GFR increased significantly in Group 2 patients. The level of RPF decreased significantly in Group 1 patients. In contrast, the level of RPF was comparable in Group 2 patients. Thus, FF returned to or approached normal values in both groups.

Discussion

Decreased FF, reflecting a relatively increased RPF, was observed frequently during the active phase of LN in this study. These haemodynamic findings may be encountered in the acute or active phase, or both, of various renal diseases; however, few reports have concentrated on renal diseases other than LN.[21–23] Several investigators have found similar haemodynamic features in LN.[12 13] However, somewhat conflicting results also have been reported previously.[14] Furthermore, clinical data that may be closely related to renal haemodynamics such as arterial blood pressure, serum albumin concentration, or the use of antihypertensive drugs and diuretics have not been clearly analysed in these studies. Thus, we evaluated the clinical value of longitudinal measurements of GFR and RPF in patients with LN.

The reduction in GFR out of proportion to that in RPF that was observed in LN has been assumed to be caused by a reduction in the capillary surface area available for filtration as a consequence of morphological changes.[18] Furthermore, increased hydrostatic pressure in proximal tubules and in Bowman's space, consequent to renal interstitial oedema, has been considered to be responsible for the decreased net ultrafiltration pressure and reduced GFR.[22] Therefore, these mechanisms may account in part for the observed renal haemodynamics in LN. However, the fact that RPF is preserved or even increased in LN does not fully support these interpretations.

Biochemical measurements and trials with prostaglandin inhibitors have suggested that vasoactive eicosanoids have a role in modulating renal haemodynamics.[24] Indeed, evidence for increased intra renal synthesis of prostaglandin has been reported in SLE.[25] If true, the relative increase in RPF during the active phase could be caused by increased intra renal synthesis or release of prostaglandin. On the other hand, several investigators have found that the urinary thromboxane B2/6-keto-PGF1 α ratio was increased in LN as compared with non-renal SLE or healthy controls.[26 27] These results suggest that other eicosanoids besides

prostaglandin may be involved in decreasing FF. Furthermore, other factors such as norepinephrine or antidiuretic hormone also may correlate with the changes in renal haemodynamics in LN.[28]

Ter Borg *et al*[18] have reported that the FF in 13 SLE patients with minimal or no disease activity was within normal limits. However, in this study, a low FF was recognised during active LN regardless of the renal histological class. Therefore, disease activity itself may play some part in the determination of the haemodynamic characteristics of LN. From results of this study, treatment with antihypertensive drugs or diuretics, or both, seem unlikely to be responsible for the decrease in FF. Although severe hypertensive patients were excluded from this study, hypertension also seemed to play little part in the serial haemodynamics changes seen here.

Both GFR and RPF have been reported to increase during the early stage of insulin dependent diabetes mellitus.[29] [30] GFR usually increases more than RPF, which results in an increased FF.[29] The predominant action of angiotensin II on the efferent arteriole compared with the afferent arteriole is thought to be responsible for this finding.[31] The observation that ACE inhibitors usually decrease the FF in insulin dependent diabetes mellitus patients supports these considerations.[29] Therefore, changes in the renin-angiotensin system may exist in patients with active LN, and may explain the relative increase in the RPF level.

Several investigators have postulated that the determination of FF in LN may be of some value in assessing the reversibility of renal function.[12] [13] In this study, low FF was recognised frequently irrespective of the degree of improvement in the GFR. LN patients with insufficient recovery of GFR also demonstrated significant improvement of urinary or immunological abnormalities, or both, as shown in table 5. Active glomerular lesions may have transformed to sclerotic lesions resulting in impaired renal function in Group 1 patients. Therefore, FF should be evaluated as one of the indices indicating disease activity or severity of LN, or both, irrespective of the GFR levels. Assessment of FF may aid in the decision to begin, continue, or stop immunosuppressive therapy in LN. After the period of this study, two patients progressed to end stage renal failure and three other patients died. However, the correlation between these haemodynamic characteristics and long term outcome of SLE patients could not be determined by this study.

Inulin clearance has been regarded as the most accurate method of measuring GFR.[32] [33] However, GFR values determined by sodium thiosulphate clearance are thought to correlate well with those ascertained by inulin clearance.[34] Recently, radiolabelled compounds have been used for the measurement of GFR or RPF, or both.[12] [13] [23] [29] At any rate, the simultaneous measurement of both GFR and RPF and relative evaluation of these parameters, namely the determination of FF, seem to be beneficial in the evaluation of LN.

In conclusion, GFR may decrease significantly in active LN, but RPF does not change or even increase. These findings seem to be characteristic of SLE patients with active renal disorders. Although further studies need to be done, FF may be a useful clinical parameter to evaluate patients with LN.

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