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Microalbuminuria in systemic sclerosis

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Abstract

A prospective study was performed to determine urinary albumin excretion in a group of 28 patients with systemic sclerosis. At the initial screen one patient had proteinuria and three had microalbuminuria. One year later these abnormalities persisted and in two of of the patients serum creatinine had significantly increased. In addition, a further three patients had developed microalbuminuria. In a control group of 10 patients with primary Raynaud's disease none had microalbuminuria. In a second control group of 16 patients with unrelated skin diseases one patient had microalbuminuria and one proteinuria, but both these patients had a history of hypertension. It is concluded that microalbuminuria is more common in patients with systemic sclerosis than in patients of equivalent age with other dermatological conditions but no vascular disease.

An increased excretion of urinary total protein is a classical hallmark of renal disease. Persistent proteinuria has also been found to be associated with increased mortality in hypertensive subjects,[1] and in the general population monitored in the Framingham study.[2] Assays for urine total protein are non-specific and insensitive and the advent of sensitive and specific assays for urinary albumin, the dominant urinary protein in patients with renal glomerular dysfunction, has enabled the detection of abnormalities at an earlier stage in the disease process. The term 'microalbuminuria' has been coined to describe an increased excretion of albumin above the reference range for healthy subjects but which is undetectable by dipstick testing.[3] This encompasses a urine albumin excretion rate of between about 20 and 200 μg/min,[4] equivalent to about 3 to 30 mg/mmol creatinine.[5]

In diabetes mellitus, microalbuminuria not only predicts the subsequent development of diabetic nephropathy[6 7] but is also associated with endothelial cell dysfunction[8] and an increased transcapillary escape rate of albumin.[9] In addition, microalbuminuria is associated with coronary heart disease, peripheral vascular disease, and essential hypertension, and is a risk factor for death from cardiovascular disease not only in diabetic patients but also in the general population.[10–15] Therefore, an increased excretion of urinary albumin may reflect not only glomerular disease but also more generalised vascular dysfunction.[16]

Systemic sclerosis is characterised by excessive collagen synthesis and microvascular changes leading to increased vascular permeability and fibrosis.[17] Whether microvascular disease is a fundamental disorder in systemic sclerosis or whether it occurs secondary to connective tissue abnormalities remains unresolved. Parallels have been drawn between the digital sclerosis of childhood diabetes and progressive systemic sclerosis, and both disorders have strong links with abnormalities of the microvascular circulation.[18] Endothelial cell damage and dysfunction are well documented in systemic sclerosis, and the prognosis and eventual outcome of the disease depend on the severity of the vascular dysfunction.[19] Renal disease carries a poor prognosis, renal failure being cited as the cause of death in 40–50% of patients, commonly preceded or accompanied by proteinuria and hypertension.[20] Patients at risk of developing vascular complications, in general, or renal dysfunction, in particular, might therefore be detected earlier by the appearance of microalbuminuria. We present here the results of our initial screening programme and a one year follow up.

Patients and methods

Urine samples were collected from 28 patients with systemic sclerosis attending the dermatology outpatient clinic. These comparised 26 women (23 white, three Afro-Caribbean—Nos 2, 8, and 10) and two men, mean age 55 years (range 34–69). Systemic sclerosis was diagnosed clinically on the basis of the American Rheumatology Association criteria[21] and the duration of symptoms was recorded. In most cases the presenting symptom was Raynaud's phenomenon. All patients except No 9 were investigated for systemic disease by chest radiography, lung function tests, a barium swallow, and an autoimmune profile. Table 1 summarises the positive results. A drug history was obtained in each case. Fifteen patients with systemic sclerosis were taking nifedipine (daily dose range 10–60 mg), primarily for its effects on impaired thrombolysis,[22] but also for its hypotensive effect in one patient (No 2). Table 1 summarises the clinical details. Two patients (Nos 7 and 24) were known to have existing renal impairment. Patient 24 had had impaired function for five years, with normal size kidneys, no ultrasound evidence of obstruction, and only inflammatory cells on urine cytology. Her EDTA clearance was 35 ml/min and her renal dysfunction was diagnosed as secondary to systemic sclerosis. Patient 7 had had impaired renal function for at least 10 years, which predated the onset of

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symptoms and diagnosis of systemic sclerosis seven years previously. An intravenous urogram failed to yield a diagnosis and a renal biopsy was not considered justifiable.

The study group was compared with 10 patients with primary Raynaud's disease (nine women, one man; mean age 45 years, range 29–57) and 16 female patients attending the dermatology outpatient clinic with unrelated skin conditions (mean age 56 years, range 40–70). The immune profile and nailfold capillaroscopy were normal in all patients with primary Raynaud's disease. Table 2 summarises the clinical details.

Infected urine samples ($>10^8$ organisms/l) were rejected. One patient (No 7) with systemic sclerosis had an acute asymptomatic urinary tract infection (UTI) and further samples were only accepted after one month of abacteriuria following treatment. In addition to these patients, one patient was not included because of recurrent UTI and three control subjects (one with Raynaud's phenomenon) were not included because of occult, asymptomatic UTI.

Blood pressure was measured with a standard mercury sphygmomanometer with the patient seated. The lower of two readings taken five minutes apart was recorded. Mean arterial pressure was calculated by adding one third of the pulse pressure to the diastolic pressure (phase V). The average mean arterial pressure was calculated on measurements repeated on separate occasions when possible. The upper limit of normal was calculated as 117 mmHg, based on a systolic blood pressure of 160 mmHg and a diastolic blood pressure of 95 mmHg.[23] One patient (No 14) was hypertensive with a mean arterial pressure of 123 mmHg. Two patients (Nos 1 and 2) and one control (No 43) were normotensive while receiving antihypertensive treatment.

Random urine samples were collected during the morning on three occasions over a period of one month. The first sample was collected in the outpatient clinic and two further samples were collected at home after seven and 14 days and posted to the laboratory. After one year the measurements were repeated in the patients with systemic sclerosis.

Albumin was assayed by radioimmunoassay[24] and urine creatinine by an endpoint Jaffe method with sample blanking. Results were expressed as albumin/creatinine ratios (mg/mmol). The upper limit of the reference range was 2·8 mg/mmol for women and 1·2 mg/mmol for men.[24] Microalbuminuria was defined as raised albumin excretion in at least two of the three samples collected.[4] Patients were classified as having overt proteinuria when their urine albumin was sufficiently high to be detectable by dipsticks (Boehringer BM test).

At the initial visit and at follow up blood was taken for full blood count, urea, creatinine, electrolytes, glucose, and liver function tests.

In four patients with systemic sclerosis and one with primary Raynaud's disease the dose of nifedipine was reduced or stopped to assess the effect on urinary albumin excretion. The blood pressure was monitored during this period of reduction with a random-zero sphygmomanometer (Hawkesley) and the blood tests were repeated.

The significance of differences between groups was assessed using the Mann-Whitney test for non-parametric data. The three male patients were excluded from this analysis because of the sex difference in albumin/creatinine ratios.

Table 1 Details of patients with systemic sclerosis at screen and one year later. All patients had Raynaud's phenomenon

Patient No	*Age*	*Duration of symptoms (years)*	*Systems affected*	*Autoantibody profile*	*MAP (mmHg)*		*Serum creatinine (μmol/l)*		*Nifedipine (mg/day)*	
					Screen	*At 1 year*	*Screen*	*At 1 year*	*Screen*	*At 1 year*
Women										
1	53	3	Skin	(ANF), cent, thyr	96	90	62	71	—	—
2	52	5	Skin	ANF, par, thyr	108	111	64	79	20	10
3	39	6	Skin	ANF	74	63	71	65	—	—
4	61	6	Skin	ANF, thyr	108	NA	74	NA	—	—
5	65	6	Skin, Oes	ANF, cent	107	86	61	64	—	60
6	59	6	Skin	ANF, cent, RAHA, latex	81	82	73	77	30	—
7	66	7	Skin	ANF, mito, RAHA, latex	101	112	136	172	—	20
8	55	>7	Skin, Oes	ANF, cent	83	90	81	90	—	10
9	66	8	Skin	cent, RAHA, latex	103	102	89	83	20	—
10	34	10	Skin, Oes	ANF	100	79	41	48	—	—
11	58	12	Skin	ANF	86	76	64	69	30	30
12	52	13	Skin, Lung	ANF	97	82	70	75	—	—
13	49	14	Skin, Oes, Lung	cent +++	96	103	77	68	60	60
14	62	15	Skin, Oes	ND	123	123	63	77	—	—
15	43	16	Skin, Oes	(ANF), cent +++	108	NA	66	NA	—	—
16	62	17	Skin, Oes, Lung	ANF +++	73	73	47	46	10	—
17	64	18	Skin	cent	85	90	73	84	60	40
18	38	18	Skin, Lung	ANF, RNP, latex, RAHA	72	NA	75	80	60	60
19	47	18	Skin	ND	107	NA	72	NA	—	—
20	69	20	Skin, Oes, Lung	ANF, Sm, latex, RAHA	109	127	97	90	40	40
21	62	20	Skin	ANF, latex, RAHA	97	100	70	71	20	20
22	56	20	Skin, Oes	ANF	93	100	77	85	30	—
23	58	20	Skin, Oes, Lung	ANF, RNP	93	100	93	129	60	60
24	64	>20	Oes, Lung	ANF, (dsDNA), (mito), latex, RAHA, thyr	107	101	142	154	—	—
25	45	>30	Skin, Lung	ANF, Sm, latex	95	87	63	70	—	30
26	68	>50	Skin	cent	82	90	64	69	60	40
Men										
27	40	9	Skin, Oes	ANF +++, RNP	85	76	77	86	40	50
28	60	>15	Skin	ANF, cent	88	79	69	72	40	40

MAP=mean arterial pressure; NA=data not available; Skin=scleroderma, telangiectasia, digital scarring, pulp resorption, ulceration; Oes=abnormal peristalsis; Lung=one or more of restrictive ventilatory defect or reduced gas transfer or bibasalar lung; ANF=antinuclear factor; dsDNA=anti-double stranded DNA; cent=anti-centromere antibody; mito=anti-mitochondrial antibody; par=anti-parietal cell antibody; RNP=anti-ribonuclear protein; thyr=anti-thyroid microsomal antibody; RAHA=rheumatoid arthritis haemagglutination test; +++=strongly positive; ( )=weakly positive; ND=none detected.

Results

Table 1 and fig 1 summarise the results for the patients with systemic sclerosis. At screening the two patients (Nos 24 and 7) with known renal impairment had raised serum creatinine values (142 and 136 μmol/l) with overt proteinuria and microalbuminuria respectively. In the remainder serum creatinine was less than 100 μmol/l (upper limit of reference range 120 μmol/l), but 2 patients (Nos 23 and 2) had microalbuminuria. Patient 2 had a history of hypertension, which predated the diagnosis of systemic sclerosis, but was normotensive on treatment with nifedipine throught the study.

One year later 27 of the 28 patients (96%) were available for follow up (table 1 and fig 1). Albumin excretion remmained abnormal in patients 24, 7, 2, and 23, though in the last case this was in the presence of a symptomatic coliform UTI and further samples were not available. In patients 7 and 23 serum creatinine had also significantly increased from 136 to 172 and from 93 to 129 μmol/l respectively. In all other patients serum creatinine differed by less than 15 μmol/l. Microalbuminuria had developed in three further patients (Nos 6, 16, and 17) and could not be explained by any change in their clinical condition or drug regimen. Patient 20 had developed hypertension (mean arterial pressure 127 mmHg), though she continued to receive nifedipine throughout the study.

Table 2 and fig 2 summarise the results for the control groups. Serum creatinine was within the reference range in all subjects. Albumin excretion was normal in all patients with Raynaud's disease and was raised in only two of the patients with unrelated skin disorders, both of whom had evidence of vascular dysfunction. Patient 43 had microalbuminuria and a history of hypertension and angina but she was normotensive on treatment with atenolol and nifedipine at the time of study. Patient 45 had overt proteinuria and a history of intermittent hypertension, though she was normotensive at the time of study. She was also receiving hormone replacement therapy.

Stopping nifedipine treatment did not seem consistently to affect urine albumin excretion (table 3), but numbers were too small for statistical analysis. Changes in mean arterial pressure appeared to be random within the normal range, probably because patients were not receiving nifedipine for its hypotensive effect.

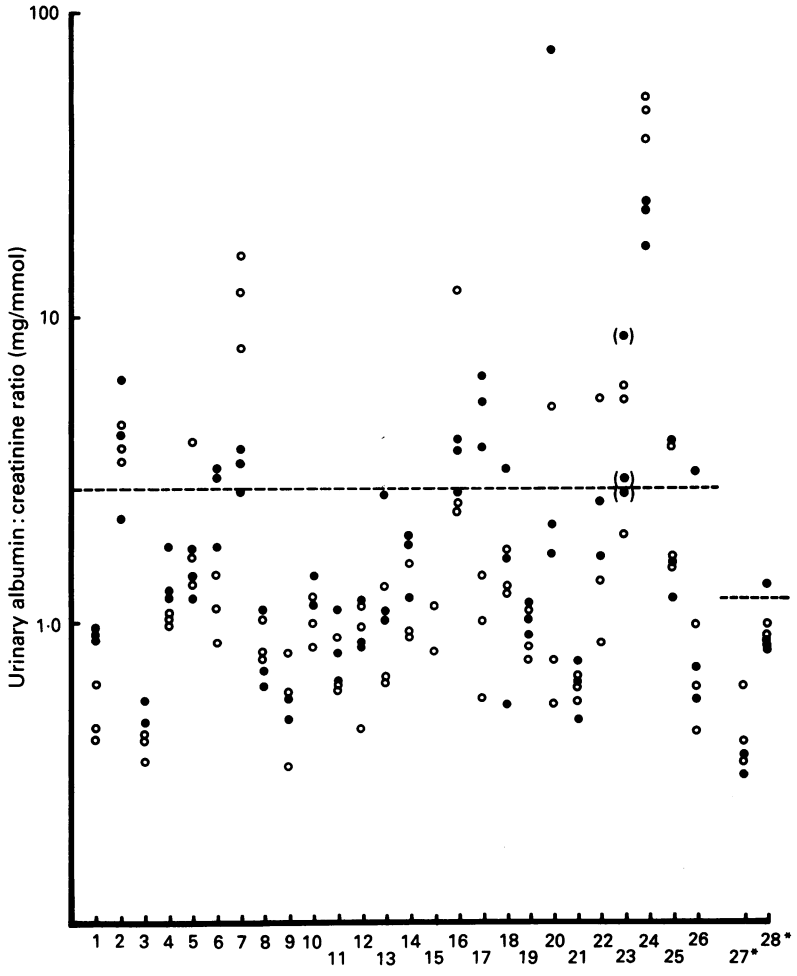

*Figure 1 Urinary albumin:creatinine ratios in patients with systemic sclerosis at screen ○ and at follow up ● one year later. Women are ranked from the left in order of increasing duration of symptoms (see table 1 for details). ---- represents the upper limit of the reference range, shown separately for men and women. (●) represents samples obtained from patient 23 in the presence of a symptomatic UTI. *Male patients.*

Table 2 Details of patients used as control groups

Patient	Age	Mean arterial pressure (mmHg)	Serum creatinine (μmol/l)	Diagnosis
29*	29	93	90	Raynaud's disease
30	40	89	83	Raynaud's disease
31	45	83	54	Raynaud's disease
32	56	100	76	Raynaud's disease
33†	46	93	56	Raynaud's disease
34	43	89	63	Raynaud's disease
35†	49	105	77	Raynaud's disease
36†	57	105	71	Raynaud's disease
37†	41	79	71	Raynaud's disease
38†	43	83	80	Raynaud's disease
39	53	87	74	Dermatitis
40	64	100	73	Actinic keratosis
41	45	93	75	Urticaria, psoriasis
42	46	78	76	Light sensitivity
43	65	90	65	Dermatitis
44	52	116	55	Urticaria
45	56	115	87	Basal cell papilloma
46	60	112	86	Melanoma
47	50	102	88	Melanocytic naevus
48	46	102	73	Viral wart
49	65	110	65	Dermatitis
50	70	100	75	Basal cell carcinoma
51	68	87	60	Mycosis fungoides
52	59	111	59	Alopecia areata
53	52	100	69	Basal cell papilloma
54	40	97	—	Dermatitis

*Male sex.
†Nifedipine.

*Table 3 Effect of nifedipine dose reduction or withdrawal on urinary albumin excretion in four patients with systemic sclerosis and one with primary Raynaud's disease (No 37)**

Patient No	Nifedipine (mg/day)	Urinary albumin/ creatinine ratio (mg/mmol)	Mean arterial pressure (mmHg)
17	20	1·5, 0·45	78
	0	11·3, 2·7	97
20	40	1·5, 1·2	105
	20	4·0, 1·2	99
21	10	0·60, 0·55	104
	0	0·72, 1·1	81
28	40	1·2, 2·1	83
	20	1·1, 0·89	83
	0	1·1, 1·6	94
37	40	1·4, 1·0	79
	20	1·9, 1·6	79
	0	0·75, 0·98	63

*The patients had been taking nifedipine for at least three months. The dose was reduced or withdrawn for two weeks and urine samples collected on two consecutive days thereafter.

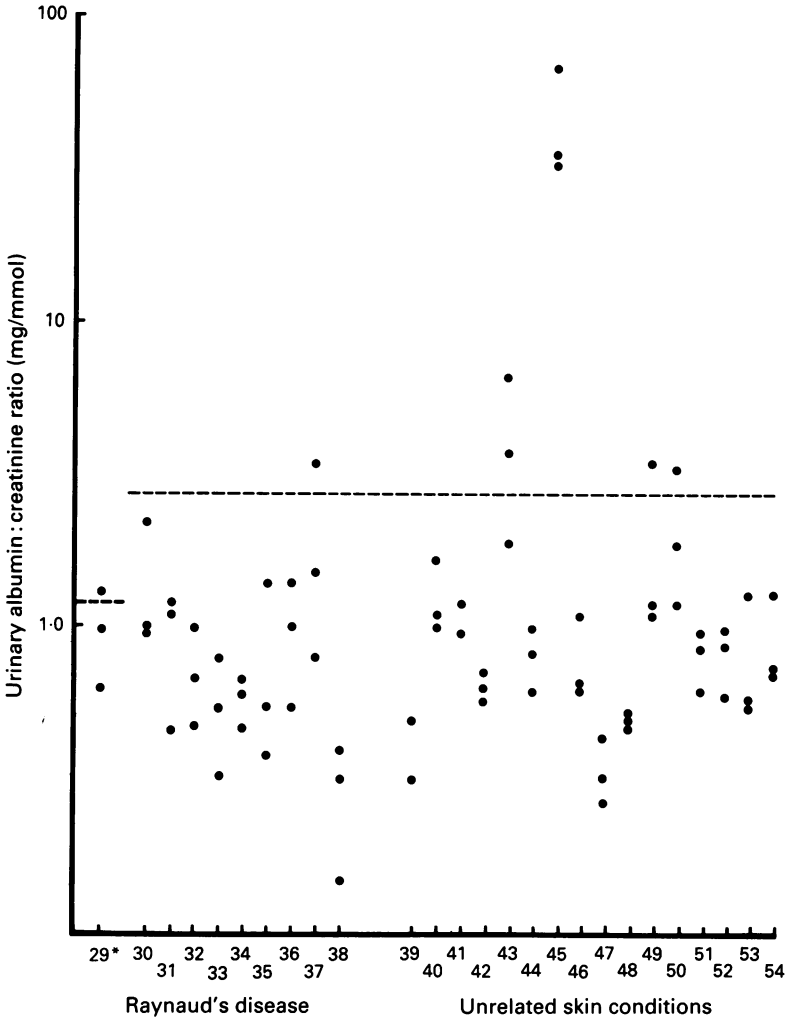

*Figure 2 Urinary albumin:creatinine ratios in 10 patients with primary Raynaud's disease and in 16 patients with unrelated skin conditions. ---- represents the upper limit of the reference range, shown separately for men and women. *Male patient.*

There was no significant difference in urinary albumin excretion between the two control groups ($p>0·05$). Urinary albumin:creatinine ratios were significantly higher in the patients with systemic sclerosis than in the control group at the initial screen ($p<0·02$) and at follow up ($p<0·001$).

No relation was apparent between disease duration and urinary albumin excretion (fig 1). At follow up the median duration of disease in seven patients with increased albumin excretion (18 years, range 6–>20) was only slightly higher than in 20 patients with a normal urine albumin (15 years, range 4–>50). Similarly, the median age of seven patients with albuminuria (63 years, range 53–67) was slightly higher than of 20 patients without (57 years, range 35–70).

Discussion

Abnormal excretion of urinary albumin was found initially in four of 28 patients with systemic sclerosis and developed in a further three patients during the course of the one year study. In one patient (No 7) renal dysfunction predated the onset of symptoms of systemic sclerosis and therefore microalbuminuria might have been due to unrelated causes. One patient (No 2) had a history of hypertension, which is known to be associated with microalbuminuria,[10] but she was normotensive during the study. In the remaining five patients no other explanation was apparent. As a group, patients with systemic sclerosis had a significantly higher excretion of urinary albumin than a control group matched for age and sex.

Urinary albumin was normal in the control group of patients with primary Raynaud's disease and was raised in only two of 16 patients with unrelated skin conditions. One of these had coexisting vascular disease and in the other there was a history of intermittent hypertension. Proteinuria has been documented in a variety of skin disorders when more than 10% of the skin is affected,[25] but none of our control group had such extensive disease.

Contradictory results have been reported about the effects of nifedipine on urinary albumin excretion, with either no change or transient increases being found.[26–29] These studies were carried out on a variety of patients with hypertension or diabetes for varying periods of time and it may not be applicable to extrapolate the results to other situations. We found no evidence to suggest that nifedipine had any effect on urinary albumin excretion in patients with systemic sclerosis.

We suggest that increased albumin excretion in patients with systemic sclerosis may reflect the underlying vascular pathology of the disorder and may also herald the onset of renal disease. In other diseses the presence of microalbuminuria carries a poor prognosis as discussed in the 'Introduction'. Whether the same prognostic information will apply in patients with systemic sclerosis requires longer term follow up, which we are continuing.

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