Albuminuria and Renal Function in Homozygous Sickle Cell Disease

Observations From a Cohort Study

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Background: The glomerular filtration rate (GFR) in homozygous sickle cell (SS) disease is supranormal in childhood but falls steeply with age, often culminating in renal failure. The risk factors underlying these observations are unclear. We therefore sought to investigate the relationships between blood pressure, renal hemodynamics, and urinary albumin excretion in subjects with SS disease and matched controls with a normal AA genotype (hereinafter, controls) as a prelude to intervention studies.

Methods: Serum creatinine level, GFR, effective renal plasma flow, blood pressure, and urinary albumin and creatinine excretion rates were measured in Jamaican individuals with SS disease aged 18 to 23 years and in controls followed from birth in a cohort study.

Results: Compared with controls, subjects with SS disease showed lower blood pressure and normal or supranormal GFR and effective renal plasma flow. Urinary albumin excretion exceeded 20 µg/min in 26% of subjects with SS disease and correlated positively with GFR and systolic blood pressure and negatively with hematocrit. A higher GFR and increased tubular secretion of creatinine combined to lower serum creatinine levels in patients with SS disease, giving an upper limit of the reference range of 0.90 mg/dL (80 µmol/L) in men and 0.77 mg/dL (68 µmol/L) in women. In addition, creatinine clearance measurements were consistently greater than GFR in subjects with SS disease.

Conclusions: The GFR remained within reference range or elevated in patients with SS disease aged 18 to 23 years. The higher GFR in patients with albuminuria was consistent with the hypothesis that high glomerular flows cause renal damage. Lower serum creatinine levels characterize patients with SS disease, and a revised clinical definition based on serum creatinine level alone is proposed.

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RENAL FAILURE IS COMMON among older patients with homozygous sickle cell (SS) disease and contributed to death in 18% of Jamaican patients older than 40 years.[1] Because the survival rate of patients is increasing,[2,3] renal failure will play a greater role in the morbidity and mortality of SS disease in the future. Renal functional abnormalities commence in early childhood, damaging the vasa rectae system, disrupting countercurrent exchange, and impairing urinary concentration (causing hyposthenuria). In patients with SS disease, glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) are increased in childhood and are associated with glomerular hypertrophy[4-6] but fall as individuals age because progressive fibrosis, focal glomerulosclerosis, and glomerular obsolescence impair renal function. In patients with diabetes mellitus, microalbuminuria has been shown to predict renal failure,[7] but it is unclear whether the albuminuria common in patients with SS disease has a similar predictive role. If so, the ability to decrease albuminuria by using angiotensin-converting enzyme (ACE) inhibitors[8,9] may protect against renal impairment.

The Jamaican Cohort Study, based on newborn screening, provides a representative sample of subjects with SS disease and controls with a normal hemoglobin (AA) genotype (hereinafter, controls) followed from birth. At the time of this study, the median age of subjects with SS disease was 20.8 years and of controls was 21.7 years, and subjects with SS disease already manifested a greater frequency and degree of albuminuria and lower serum creatinine levels. The factors underlying these observations are unclear. We there-

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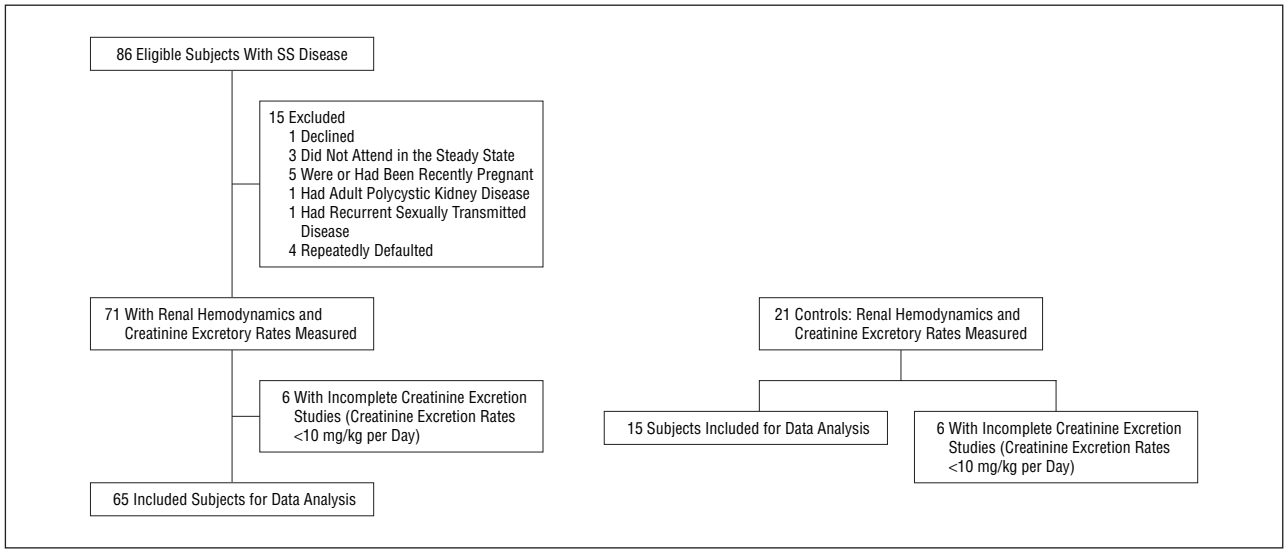

Figure 1. Flowchart showing enrollment of subjects for renal hemodynamics and creatinine clearance measurements. Subjects with normal (AA) genotype are indicated as controls; SS indicates homozygous sickle cell disease.

fore sought to investigate the relationship between blood pressure, renal hemodynamics, and urinary albumin excretion in subjects with SS disease and matched controls as a prelude to intervention studies. A secondary objective was to examine the distribution of serum creatinine levels and the agreement between creatinine clearance measurement and glomerular filtration to determine whether creatinine clearance measurements could be used as a proxy for glomerular filtration in clinical practice and longitudinal studies of SS disease.

METHODS

PATIENTS

The patients attended the Sickle Cell Clinic of the University Hospital of the West Indies, Kingston, Jamaica, and participated in the Jamaican Cohort Study from birth. The study was based on all cases of SS disease among 100 000 nonoperative deliveries at the main government maternity hospital (Victoria Jubilee Hospital, Kingston) screened from July 1973 to December 1981. A total of 311 babies with SS disease were recruited into the study,[10] of whom the first 125 were each matched with 2 controls of the same sex, born closest in time to the index case, but with an AA genotype. During the study period (November 1995 to May 1997), 86 patients with SS disease were 18½ years or older and lived in the Kingston area; of these patients, 15 were excluded for various reasons and an additional 6 had incomplete creatinine excretion studies, leaving 65 patients with complete data (**Figure 1**). Of 21 randomly selected controls, 6 had incomplete creatinine excretion studies, leaving 15 with complete data.

PROCEDURES

In these patients, SS disease was diagnosed at birth[11] and confirmed later by standard techniques.[12] Height was measured with a wall-mounted stadiometer, and weight was measured on a lever balance. In a preliminary study, the distribution of serum creatinine levels was assessed by measurements taken on each subject's 18th birthday. Renal function studies were performed over an 18-month period, measuring urine-specific gravity by hydrometry and semiquantitative proteinuria by dipstick on a freshly voided sample. After 1 hour of recumbence, 3 measurements of sitting blood pressure and pulse rates were taken at 5-minute intervals using a Dynamap (model 1846 SX; Critikon Co, Tampa, Fla), a widely used automated blood pressure recording system that uses plethysmography and algorithms for depicting blood pressure. Urinary albumin was measured by radioimmunoassay[13] and creatinine by the rate-dependent Jaffe reaction. Effective renal plasma flow was calculated from the decay curve[14] after injection of 0.027 mCi (1 MBq) of iodine I 125–labeled hippuran (a solution of iodohippurate usually linked to an iodine isotope, either iodine I 131 or I 125, and used in the determination of ERPF), in the antecubital vein of one arm, and samples were taken through a cannula in the other arm at 5, 10, 15, 20, 30, 40, 50, and 60 minutes. The GFR was calculated from the decay curve[15] after an injection of 0.081 mCi (3 MBq) of chromium Cr 51–labeled EDTA into the first arm and samples were taken at 2, 3, 4, and 5 hours (a 24-hour sample was taken in 1 patient in whom a low GFR was suspected). Effective renal blood flow (ERBF) was calculated as ERPF/(1 – hematocrit). Measurements of GFR followed that of ERPF.

PROTOCOL

A diet containing no cooked meat was commenced on the day before and continued throughout the study period. Studies were performed over a 6-hour period (between 8:30 AM and 5 PM) on 2 days, usually consecutively but always within a 5-day period. On day 1, height and weight were measured, and the bladder was emptied and the initial midstream urine sample tested for specific gravity, proteinuria, and hematuria. Urine microscopy was performed and a blood sample was taken for hematologic and biochemical testing. With the subjects allowed unrestricted fluid but asked to drink at least 100 mL/h, a 6-hour urine collection was taken for measurement of albumin and creatinine excretion rates. The ERPF and GFR were measured and standardized for body surface area (1.73 m^2). On day 2, a 6-hour urine collection was taken for measurement of creatinine excretion rates after administration of cimetidine at doses of 400 mg ($t = -3$ hours), 200 mg ($t = 0$), and 200 mg ($t = +3$ hours). Plasma creatinine was averaged at $t = 0$ and $t = +6$ hours to calculate the cimetidine creatinine clearance. The study was ap-

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proved by the ethical committee of the University Hospital of the West Indies, and each patient signed a consent form after receiving verbal and written explanation of the study details.

STATISTICAL METHODS

Sex composition was assessed using the binomial exact test. Genotype differences in anthropometric, hematologic, and biochemical findings; blood pressure measurements; and renal hemodynamics were assessed using the distribution-free Mann-Whitney test. The albumin excretion rate (AER) was heavily skewed[16] and was transformed to improve its normality using a Box-Cox power transformation.[17] Potential predictors of this transformed AER were then explored using linear regression. Predictors of AER were selected using a manual stepwise procedure after adjusting for age and sex. The agreement between GFR and creatinine clearance was examined using limits of agreement.[18] Using this procedure, the size of the limits-of-agreement reference lines and any values beyond these limits are of specific interest, and the final decision about what is an acceptable level of agreement is a clinical one.

Table 1. Serum Creatinine Levels at Age 18 Years in 116 Subjects With SS Disease and in 123 Controls*

Genotype	Sex, No.	Mean (95% CI), mg/dL	Upper Limit, mg/dL
Controls	M, 58	0.89 (0.84-0.96)	1.39
	F, 65	0.69 (0.65-0.74)	1.05
Subjects with SS disease	M, 62	0.50 (0.44-0.54)	0.90
	F, 54	0.43 (0.39-0.48)	0.77

Abbreviations: CI, confidence interval; SS, homozygous sickle cell.
SI conversion factor: To convert to micromoles per liter, multiply by 88.4.
*Those with normal (AA) genotype.

RESULTS

PROSPECTIVE RENAL STUDY

In the preliminary study, the distribution of serum creatinine levels measured on the subjects' 18th birthday (116 individuals with SS disease and 123 controls) indicated lower levels in subjects with SS disease (**Table 1**).

Baseline characteristics of subjects with SS disease and controls (**Table 2**) show that height did not differ between the genotypes, but weight, body surface area, body mass index, and age were lower in subjects with SS disease. As expected, subjects with SS disease had lower total hemoglobin; higher platelet counts, total nucleated cell counts, and bilirubin levels; lower diastolic and mean arterial blood pressures; and higher pulse rates but no difference in systolic blood pressure. Serum creatinine and urea levels were lower in subjects with SS disease, but the differences in uric acid, sodium, potassium, or albumin levels between the 2 study genotypes did not reach statistical significance.

The GFR, ERPF, and calculated ERBF were increased in both male and female subjects with SS disease compared with sex-matched controls (**Table 3** and **Table 4**). Filtration fraction was significantly lower in male subjects with SS compared with male controls but did not differ in female subjects compared with female controls. Urine-specific gravity was lower in subjects with SS disease compared with controls. In male subjects with SS disease, urine flow rates were significantly greater than in male controls during creatinine clearance measurements, but the 2 groups did not differ during cimetidine creatinine clearance. In female subjects with

Table 2. Clinical Characteristics of Subjects

	Subjects With SS Disease (33 Men and 32 Women)				Controls* (8 Men and 7 Women)				Mann-Whitney Test,
Variables	No.	Med	Min	Max	No.	Med	Min	Max	*P* Value
Age, y	65	20.8	18.5	23.4	15	21.7	21.0	22.9	.002
Height, cm	65	168.9	144.5	188.9	15	167.0	151.4	181.5	.98
Weight, kg	65	55.0	34.0	75.5	15	68.1	48.2	101.2	<.002
Body surface area, m^2	65	1.6	1.2	2.0	15	1.8	1.5	2.3	<.005
BMI	65	18.6	14.5	26.8	15	22.4	18.9	33.1	<.001
Hemoglobin, g/dL	65	7.7	4.8	11.1	15	13.4	7.7	15.8	<.001
Nucleated cell count, $\times 10^9$/L	65	11.1	4.2	93.6	15	4.9	3.5	6.6	<.001
Platelet count, $\times 10^6$/μL	65	449 000	123 000	896 000	15	229 000	180 000	313 000	<.001
Total bilirubin, mg/dL	65	3.0	0.6	19.4	15	0.7	0.2	3.5	<.001
Urea nitrogen, mg/dL	65	11.4	3.6	69.1	15	19.8	6.0	35.4	<.001
Creatinine, mg/dL	65	0.51	0.15	1.74	15	0.83	0.54	1.19	<.001
Uric acid, mg/dL	65	53.8	20.2	106.0	14	43.7	21.9	68.9	.06
Albumin, g/L	65	46.0	33.0	53.0	14	45.5	39.0	50.0	.51
Serum sodium, mmol/L	65	141	136	144	14	141	138	146	.28
Serum potassium, mmol/L	65	4.6	3.4	6.1	14	4.5	3.5	4.9	.08
BP, mm Hg									
Systolic	65	103	85	153	15	110	95	144	.09
Diastolic	65	58	42	100	15	68	55	84	<.001
Mean	65	76	60	123	15	84	70	102	<.003
Pulse rate, beats/min	65	69	53	171	15	63	44	76	<.001

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BP, blood pressure; max, maximum value; med, median value; min, minimum value; SS, homozygous sickle cell.
SI conversion factors: To convert bilirubin, creatinine, urea nitrogen, and uric acid to millimoles per liter, multiply by 17.1, 88.4, 0.357, and 59.485, respectively.
*Those with normal (AA) genotype.

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Table 3. Renal Hemodynamics and Urinary Measures in Male Subjects

	Subjects With SS Disease				Controls, Mann-Whitney Test*				
Variables	No.	Med	Min	Max	No.	Med	Min	Max	*P* Value
GFR, mL/min per 1.73 m^2	32	137	21	210	8	105	89	123	<.005
ERPF, mL/min per 1.73 m^2	30	879.5	175.0	1314.0	8	490.5	269.0	588.0	<.001
ERBF, mL/min per 1.73 m^2	30	1132	198	1663	8	839	516	996	<.001
FF, %	30	16	11	24	8	22	19	33	<.001
Specific gravity	33	1.010	1.002	1.014	8	1.022	1.018	1.030	<.001
UFR during creatinine excretion, mL/min	33	1.6	0.7	2.7	8	0.8	0.5	1.7	<.005
UFR during cimetidine CrCl, mL/min	33	1.8	0.8	4.1	8	1.8	0.9	4.3	.92
Creatinine excretion, mmol/kg per day	33	0.17	0.13	0.34	8	0.17	0.16	0.19	.77
Cimetidine creatinine excretion, mmol/kg per day	33	0.15	0.10	0.19	8	0.14	0.09	0.18	.58
CrCl, mL/min per 1.73 m^2	33	144.0	32.5	419.0	8	91.0	79.0	99.0	<.001
Cimetidine CrCl, mL/min per 1.73 m	33	114	20	216	8	69	46	113	<.002
Albumin excretion rate, µg/min	33	8.3	2.4	666.8	8	5.4	3.5	7.64	<.03
Albumin creatinine ratio, mg/mmol	33	1.5	0.4	193.5	8	0.5	0.4	1.0	<.002

Abbreviations: CrCl, creatinine clearance; ERBF, effective renal blood flow; ERPF, effective renal plasma flow; FF, filtration fraction; GFR, glomerular filtration rate; max, maximum value; med, median value; min, minimum value; SS, homozygous sickle cell; UFR, urine flow rate.
SI conversion factor: To convert creatinine clearance to microliters per second, multiply by 0.01667.
*Those with normal (AA) genotype.

Table 4. Renal Hemodynamics and Urinary Measures in Female Subjects

	With SS Disease				Controls, Mann-Whitney Test*				
Variable	No.	Med	Min	Max	No.	Med	Min	Max	*P* Value
GFR, mL/min per 1.73 m^2	32	126	77	263	7	117	90	130	.06
ERPF, mL/min per 1.73 m^2	31	848	558	1447	6	647	524	885	<.008
ERBF, mL/min per 1.73 m^2	31	1058.0	755.0	1809.0	6	939.5	783.0	1361.0	.19
FF, %	31	16	10	28	6	19	13	20	.36
Specific gravity	32	1.010	1.001	1.014	7	1.020	1.014	1.023	<.001
UFR during creatinine excretion, mL/min	32	1.3	0.5	7.6	7	1.5	0.7	2.9	.94
UFR during cimetidine CrCl, mL/min	32	1.8	0.8	6.5	7	1.6	0.7	4.6	.58
Creatinine excretion, mmol/kg per day	32	0.14	0.11	0.28	7	0.15	0.13	0.2	.09
Cimetidine creatinine excretion, mmol/kg per day	32	0.13	0.1	0.17	7	0.14	0.1	0.17	.49
CrCl, mL/min per 1.73 m^2	32	145	71	262	7	106	88	129	<.005
Cimetidine CrCl, mL/min per 1.73 m^2	32	109	58	236	7	82	72	113	<.02
Albumin excretion rate, µg/min	32	11.0	2.6	707.1	7	4.3	2.4	8.5	<.001
Albumin creatinine ratio, mg/mmol	32	2.1	0.00	131.5	7	0.7	0.4	1.8	<.006

Abbreviations: CrCl, creatinine clearance; ERBF, effective renal blood flow; ERPF, effective renal plasma flow; FF, filtration fraction; GFR, glomerular filtration rate; max, maximum value; med, median value; min, minimum value; SS, homozygous sickle cell; UFR, urine flow rate.
SI conversion factor: To convert creatinine clearance to microliters per second, multiply by 0.01667.
*Those with normal (AA) genotype.

SS disease, urine flow rates during creatinine clearance measurements with or without cimetidine administration did not differ from the female controls. Urinary creatinine excretion, with and without cimetidine administration, did not differ between the 2 groups when compared within patients of the same sex. Creatinine clearance was systematically lower than GFR in controls (mean difference, –13.5 mL/min [0.2 mL/s]; 95% limits of agreement, –43.2 to 16.1). In contrast, creatinine clearance was systematically greater in subjects with SS genotype. Among subjects with SS disease, the magnitude of the difference between creatinine clearance and GFR increased as GFR increased, ranging from an average of –76.3 (95% confidence interval, –171 to 18) at the minimum recorded GFR to 138.6 (range, 43.9-233.3) at the maximum recorded GFR (**Table 5**, **Figure 2**A and B). The systematic difference between creatinine clearance measured with cimetidine and GFR was clearer; creatinine clearance was systematically less than GFR in both subjects with SS disease (mean difference, –20.9; 95% limits of agreement, –91.0 to 49.2) and controls (mean difference, –29.7; 95% limits of agreement, –69.1 to 9.6) (Table 5 and Figure 2C and D).

The relationship between GFR and serum creatinine in the 2 study groups is shown in **Figure 3**. Renal impairment was uncommon in these subjects with SS disease; only 1 patient satisfied the traditional definition, a patient with SS disease aged 19 years (creatinine level, 1.74 mg/dL [154 µmol/L]; GFR, 21 mL/min per 1.73 m^2), and 2 more (1 man and 1 woman) satisfied the more rigorous definition of having creatinine levels of 0.90 and 0.77 mg/dL (80 and 68 µmol/L), respectively.

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Table 5. Limits of Agreement of Creatinine Clearance and GFR Determined by Plasma Clearance of Chromium Cr 51 EDTA*

	Creatinine Clearance		Creatinine Clearance With Cimetidine	
LA	Subjects With SS Disease	Controls†	Subjects With SS Disease	Controls†
Min GFR	−76.3 (−171.0 to 18.4)	−14.2 (−43.8 to 15.4)	−22.7 (−91.4 to 46.0)	−44.2 (−79.5 to −8.9)
Max GFR	138.6 (43.9 to 233.3)	−13.2 (−42.9 to 16.4)	−19.2 (−87.9 to 49.5)	−15.9 (−51.2 to 19.4)
Global LA	25.9 (−94.5 to 146.4)	−13.5 (−43.2 to 16.1)	−20.9 (−89.6 to 47.8)	−29.7 (−68.3 to 8.8)

Abbreviations: GFR, glomerular filtration rate; LA, limits of agreement; max, maximum; min, minimum; SS, homozygous sickle cell.
*Values are given as mean differences (95% confidence intervals).
†Those with normal (AA) genotype.

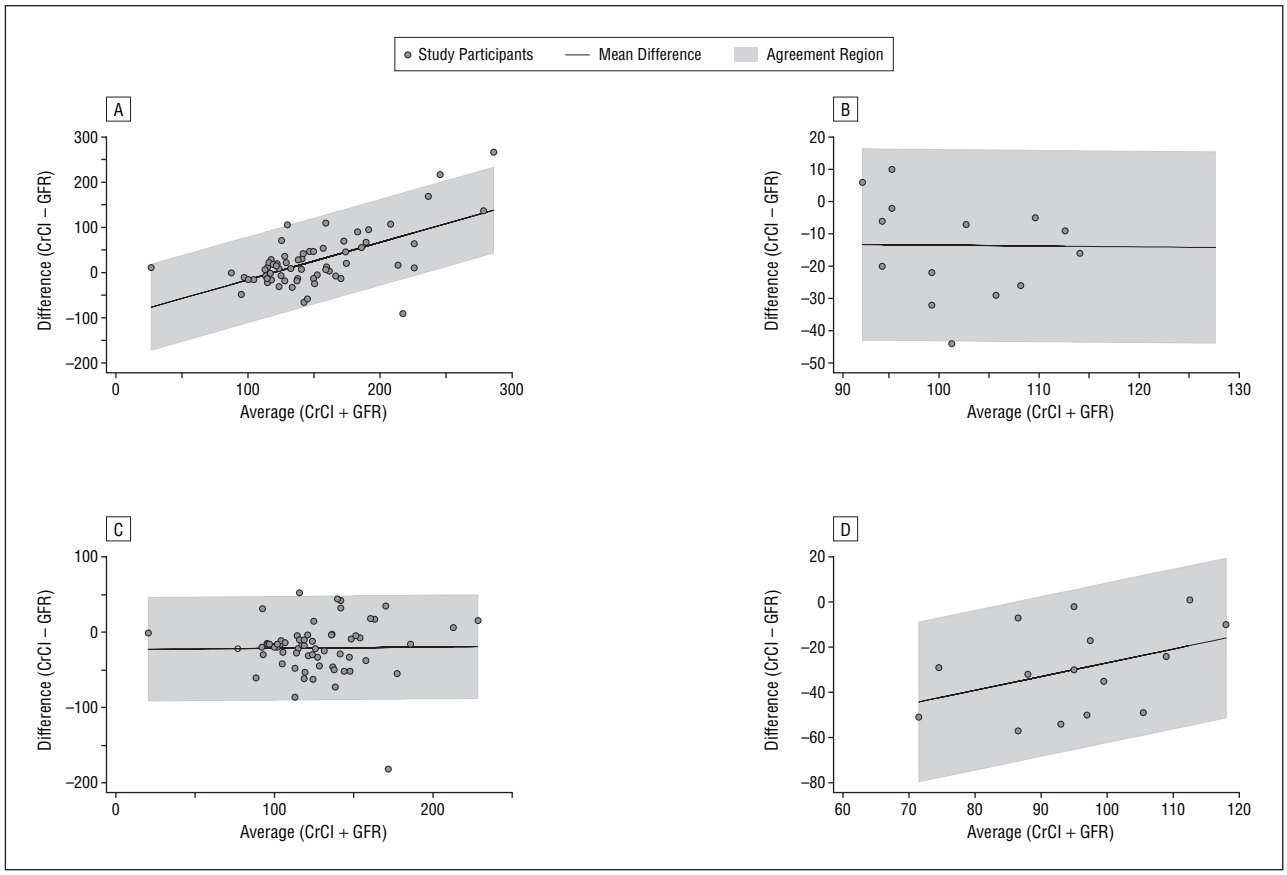

Figure 2. Limits-of-agreement plots of creatinine clearance (CrCl) and glomerular filtration rate (GFR) determined by plasma clearance of chromium Cr 51–EDTA (ethylenediaminetetraacetic acid). A, participants with homozygous sickle cell (SS) disease; B, controls; C, participants with SS disease, creatinine clearance measured with cimetidine; and D, controls, creatinine clearance measured with cimetidine.

COMPARISON OF SUBJECTS WITH VS WITHOUT ALBUMINURIA

Albumin excretion rate and albumin-creatinine excretion ratio were greater in both male and female subjects with SS genotype compared with sex-matched controls (Table 3 and Table 4). However, albumin excretion rates in controls did not exceed 11.8 µg/min, so an arbitrary AER of 20 µg/min was used to identify the subjects with SS disease as having (AER≥20 µg/min; n=17) or not having (AER<20 µg/min; n=48) albuminuria. On one hand, there were no differences in sex; age; height; weight; body surface area; body mass index; or hematologic, electrolyte, or biochemical indices (data not shown). On the other hand, systolic, diastolic, and mean arterial pressures and GFR were higher in subjects with albuminuria (**Table 6**). Regression analysis showed that albumin excretion rate correlated positively with systolic blood pressure and GFR standardized for body surface area, and negatively with serum sodium and hematocrit (**Table 7**).

COMMENT

Serum creatinine levels were lower in subjects with SS disease compared with controls, and a more sensitive indicator of renal impairment is proposed as 0.90 mg/dL (80 µmol/L) for men and 0.77 mg/dL (68 µmol/L) for women based on an upper limit of the reference range, derived from 2 SDs above mean values. The traditional

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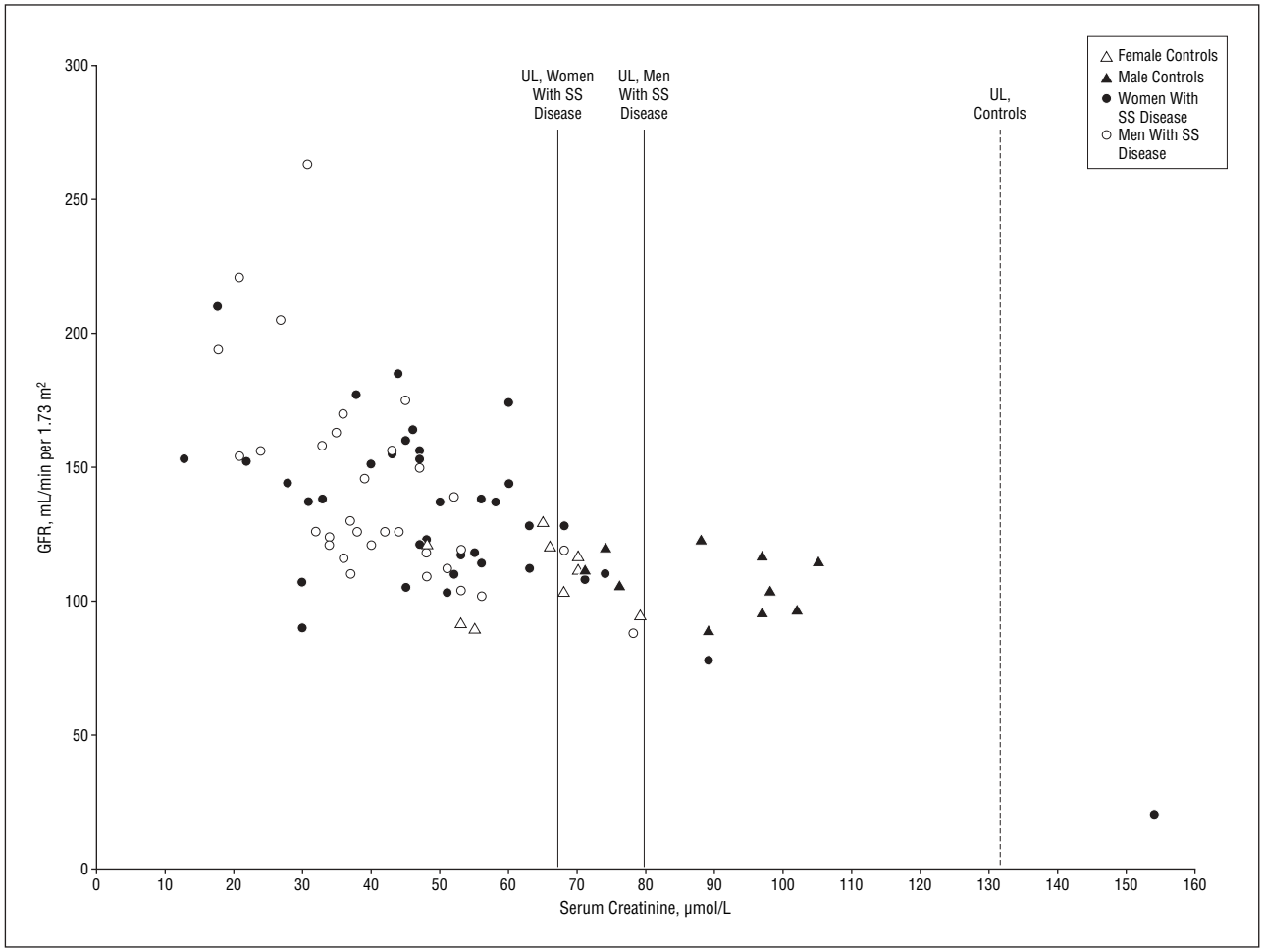

Figure 3. Relationship between glomerular filtration rate (GFR) and serum creatinine levels in subjects with homozygous sickle cell (SS) disease and those with normal (AA) genotype (controls). UL indicates upper limit. To convert SI units to milligrams per deciliter, divide by 88.4.

definition of a serum creatinine level higher than 1.49 mg/dL (>132 μmol/L) seriously underestimates the frequency and severity of renal impairment in subjects with SS disease and may explain the apparently paradoxical observation that a falling hemoglobin level preceded the onset of renal failure reported in a study by Powars et al,[19] because such patients are likely to already have severe renal impairment. This American study[19] also differed from the Jamaican experience in the reported early age of renal impairment (median age, 23 years), which may have resulted from the biases inherent in a symptomatically acquired population. Defining new upper limits for serum creatinine in patients with SS disease will allow earlier recognition of renal failure and cautions the use of potentially nephrotoxic therapies such as nonsteroidal anti-inflammatory drugs and aminoglycosides.

The level of serum creatinine is inversely related to GFR and is also affected by factors independent of GFR, which include age, sex, race, body size, and diet.[20,21] In this study, serum creatinine levels in subjects with SS disease were lower than predicted from the inverse relationship between GFR and serum creatinine. In subjects with SS disease, the GFR was approximately 19% greater than that of controls, yet the serum creatinine level was approximately 40% lower, which suggests that the changes in GFR alone could not account for the lower serum creatinine values. In the steady state, the rate of creatinine generation approximates to creatinine excretion, and the similar creatinine excretion in subjects with SS disease and in sex-matched controls when standardized for body weight suggests that the intake of protein was not different in the 2 groups. This is consistent with nutritional studies in the Jamaican Cohort Study, which noted similar protein intake in subjects with SS disease and in controls.[22,23] Our data also show that the contribution of tubular creatinine secretion to creatinine clearance was greater in subjects with SS disease compared with controls (~29% vs 17%), and it seems likely that this, as well as the increased GFR, contributes to the lower serum creatinine in subjects with SS disease.

In SS disease, GFRs are high in early childhood and decline with age, although the steep rate of decline noted in earlier studies[5] may have been influenced by patient selection. A high GFR persisted at the median age of 20.8 years in subjects with SS disease in the present study, even when corrected for the genotype difference in body surface area, and is more consistent with observations elsewhere[6] that a high GFR persists in most young adult patients with SS disease. Effective renal plasma and blood flows were all significantly elevated in subjects with SS disease, although the technique of measurement assumes that the marker is similarly distributed in both genotypes, an

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Table 6. Some Clinical and Renal Hemodynamic Features in Subjects With SS Disease With vs Without Albuminuria

Variables	With Albuminuria (9 Men and 8 Women)				Without Albuminuria (24 Men and 24 Women)				Mann-Whitney Test, *P* Value
	No.	Median	Min	Max	No.	Median	Min	Max	
BP, mm Hg									
Systolic	17	110	92	153	48	102	85	135	<.008
Diastolic	17	61	53	100	48	58	42	80	<.03
Mean	17	80	69	123	48	75	60	101	<.04
Pulse rate, beats/min	17	68	54	97	48	70	53	101	.31
Specific gravity	17	1.009	1.005	1.012	48	1.010	1.001	1.014	.22
AER, µg/min	17	99	27	707	48	7	2	18	<.001
ACR, mg/mmol	17	13.7	3.0	193.5	48	1.32	0.00	3.38	<.001
GFR, mL/min per 1.73 m^2	17	154	21	263	47	126	77	210	<.02
ERPF, mL/min per 1.73 m^2	17	917	175	1314	44	861	558	1447	.36
ERBF, mL/min per 1.73 m^2	17	1142	198	1677	44	1087	755	1809	.36
FF, %	17	17	11	28	44	15	10	24	.18

Abbreviations: ACR, albumin-creatinine ratio; AER, albumin excretion rate; BP, blood pressure; ERBF, effective renal blood flow; ERPF, effective renal plasma flow; FF, filtration fraction; GFR, glomerular filtration rate; max, maximum value; min, minimum value; SS, homozygous sickle cell.

assumption supported by the similar regressions between GFR and creatinine in subjects with SS disease and controls.

The measurement of GFR by the plasma clearance of chromium Cr 51–EDTA has been validated against inulin clearance in subjects with varying degrees of renal dysfunction,[24] but the use of creatinine clearance as a marker of GFR is affected by tubular secretion and reabsorption.[20] Creatinine secretion occurs in the proximal tubules, and creatinine clearance tends to overestimate GFR by an amount equivalent to tubular clearance of creatinine. In this study, creatinine clearance overestimated GFR in subjects with SS disease but underestimated GFR in controls. Because tubular clearance of creatinine is competitively inhibited by cimetidine, an oral cimetidine protocol has been reported to improve the precision of creatinine clearance estimates of GFR.[25,26] However, in this study, cimetidine creatinine clearances, although consistently higher in subjects with SS disease, underestimated GFR compared with chromium Cr 51–EDTA derived values in both genotypes. Potential sources of inaccuracy in estimation of GFR in this study include the short creatinine clearance protocol employed (6 vs 24 hours), which may magnify the errors from incomplete bladder emptying, from low urine flow rates, or from tubular reabsorption, and the assays of plasma creatinine, which become increasingly inaccurate at low concentrations, causing large errors in clearance calculations. Whatever the reasons, the use of the cimetidine creatinine clearance in the present study did not improve the accuracy of GFR estimation.

Defining albuminuria on the basis of albumin excretion rates greater than 20 µg/min gave an overall prevalence of 17 (26%) of 65 subjects with SS disease. Intuitively, the greater prevalence of albuminuria in subjects with SS disease might have been expected to reflect renal damage and a diminished GFR, but the association with a higher GFR raises the possibility that hyperfiltration may contribute to renal damage. The ACE inhibitors reduce albuminuria in SS disease[8,9] without any measurable change in mean arterial pressure, GFR, or ERPF. In healthy volunteers and in patients with essential hypertension, ACE inhibitors increase renal plasma flow and are known to decrease renal vascular resistance, especially in the postglomerular arterioles. The resulting fall in intraglomerular pressure seems to be the mechanism that reduces proteinuria in subtotally nephrectomized rats.[27] A reduction in proteinuria while receiving ACE inhibitors has been reported in short-[28] and longer-term[29] studies in diabetic nephropathy and in other renal diseases.[30] The reduction in proteinuria observed in SS disease was for shorter periods—2 weeks[8] and 6 months[9]—and longer-term studies are needed to assess the effect of ACE inhibitors on the progression of renal impairment in SS disease. Such trials are vital because if the primary mechanism for the renal impairment in subjects with SS disease is a progressive glomerular fibrosis secondary to repeated vascular damage by the abnormal red cells, the reduction in proteinuria and relief of intraglomerular hypertension by ACE inhibitors may have a beneficial effect on long-term progression of the glomerular disease.

Table 7. Factors Associated With Albuminuria* in Subjects With SS Disease

Variable	Coefficient (95% CI)†	*P* Value
Age, y	4.76 (−8.83 to 18.35)	.49
Sex	5.46 (0.19 to 10.73)	.04
GFR, mL/min per 1.73 m^2	0.40 (0.20 to 0.60)	<.001
Systolic BP, mm Hg	1.28 (0.69 to 1.88)	<.001
Hematocrit	−2.93 (−4.59 to −1.27)	.001
Serum sodium, mmol/L	−3.18 (−6.44 to 0.07)	.06

Abbreviations: BP, blood pressure; CI, confidence interval; GFR, glomerular filtration rate; SS, homozygous sickle cell.

*Albuminuria values transformed in regression by Box-Cox[17] transformation to improve normality.

†Model building performed after preadjustment for age and sex.

Serum sodium concentrations reflect the balance between total body water balance as well as sodium intake

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and excretion. Several studies[31,32] have reported that sodium and water retention are important in the initiation and maintenance of systemic hypertension in subjects with diabetes mellitus and with microalbuminuria and overt nephropathy. Our findings of higher systemic blood pressure in subjects with SS disease with vs without albuminuria, as well as the relationship of serum sodium to albuminuria, indicate that a similar pathologic mechanism may be operating in subjects with SS disease and albuminuria.

The short-term, cross-sectional nature of the present study does not allow analysis of longitudinal effects but provides a "snapshot" of renal function in young adults. This picture supports a revision of the definition of renal impairment in subjects with SS disease; shows that albuminuria already occurs in over a quarter of the subjects and that mean GFR, ERPF, and ERBF remain supranormal although renal failure had already occurred in 1 patient; and identifies some of the factors associated with albuminuria. The relationship between albuminuria and subsequent renal failure will be clarified on longer-term follow-up of the Jamaican Cohort Study.

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