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POSTER ABSTRACTS

114.SICKLE CELL DISEASE, SICKLE CELL TRAIT AND OTHER HEMOGLOBINOPATHIES, EXCLUDING THALASSEMIAS: CLINICAL AND EPIDEMIOLOGICAL

Persistent Albuminuria and Chronic Kidney Disease in Adults with Sickle Cell Disease: Results from a Multicenter Natural History Study

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Background:
Patients with sickle cell disease (SCD) are at high risk for developing kidney disease. Albuminuria, an early marker of kidney injury, may be initially transient in patients with SCD. Existing guidelines propose confirming albuminuria at multiple time-points before intervention. A recent study suggests a urinary albumin-creatinine ratio (UACR) $\geq$ 100 mg/g correlates highly with persistent albuminuria and subsequent decline in estimated glomerular filtration rate (eGFR). We examined a cohort of patients with SCD to assess those characteristics associated with persistent albuminuria and chronic kidney disease (CKD).
Methods
During routine clinical visits, we enrolled patients with HbSS or HbSß ^{0} thalassemia between 18 and 65 years at 4 centers into a prospective study to assess the natural history of kidney disease in SCD. We excluded patients if they had bone marrow transplantation, cancer, connective tissue disease, diabetic nephropathy, other glomerular diseases, hepatitis (B or C), HIV, or were on dialysis. Blood and urine were collected for routine clinical laboratory assessments. Serum cystatin C was measured by commercially available ELISA, and eGFR was calculated using the CKD-EPI-2012 cystatin C equation. We defined CKD as an eGFR $<$ 60 mL/min/1.73m ^{2} or presence of albuminuria. Glomerular hyperfiltration was defined as an eGFR$>$130 in females and $>$140mL/min/1.73m ^{2} in males, respectively. Persistent albuminuria was considered present if 2 or 3 UACR values were $\geq$30 mg/g or if initial baseline value was $\geq$100 mg/g (PMID: 32289161). We utilized generalized linear models adjusting for age and sex to identify characteristics associated with persistent albuminuria and CKD. For multivariable selection, we fit binomial or multinomial LASSO regression models adjusted for age, sex, hemoglobin, %Hemoglobin F, hemoglobinuria, and hydroxyurea to identify those variables associated with outcomes of interest.
Results
Of 284 enrolled patients, 268 had complete data for UACR, cystatin C and serum creatinine at baseline; 104 (38.8%) of these had persistent albuminuria (Table 1). CKD was present in 40.7% of patients and 26.5% exhibited hyperfiltration. In analyses adjusted for age and sex, several factors were associated with the likelihood of persistent albuminuria. Higher hemoglobin, higher %Hemoglobin F, higher serum bicarbonate and use of NSAIDs were associated with decreased likelihood of persistent albuminuria. Higher systolic and diastolic blood pressure, elevated serum alkaline phosphatase, total bilirubin, and

white blood cell count (WBC) were associated with an increased likelihood of persistent albuminuria as were presence of hemoglobinuria and use of angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB). In multivariable selection, higher systolic and diastolic blood pressure, ACEi/ARB use, leg ulcers, higher WBC, higher aspartate transaminase (AST) remained associated with higher likelihood of persistent albuminuria. Presence of avascular necrosis, NSAID use, and higher serum bicarbonate were associated with lower likelihood of persistent albuminuria. When evaluating baseline UACR, individuals with UACR≥100 mg/g had similar probability of subsequent albuminuria as compared to those with severe albuminuria (UACR≥300 mg/g) [Table 2].

Conclusion

Persistent albuminuria in this cohort was associated with multiple clinical features. Lower use of NSAIDs in this cohort likely represents counseling of patients to avoid these due to their kidney disease. The relationship with serum bicarbonate suggests a propensity for metabolic acidosis in these patients which could exacerbate the underlying SCD. These data confirm the predictive value of a single UACR value ≥100 mg/g for persistent albuminuria, suggesting this may be a sufficient trigger to warrant intervention. CKD, hyperfiltration and albuminuria were extraordinarily common, consistent with prior studies and validate use of this cohort for additional longitudinal assessment of kidney disease in SCD.

Disclosures Derebail: *Amgen:* Consultancy; *Novartis:* Consultancy; *Forma Therapeutics:* Consultancy; *Travere Therapeutics:* Consultancy; *Pfizer:* Consultancy; *Bayer:* Consultancy; *UpToDate:* Patents & Royalties. **Desai:** *Novartis:* Research Funding, Speakers Bureau; *NIH:* Research Funding; *PCORI:* Research Funding; *University of Pittsburgh:* Research Funding; *Chiesi:* Consultancy; *US Food & Drug Administration:* Research Funding; *University of Tennessee:* Research Funding; *Forma Therapeutics:* Consultancy; *Vertex:* Consultancy; *POC Detection of Hemoglobin Sickling via Magnetic Fractionation:* Patents & Royalties: (Pending). **Ataga:** *FDA:* Research Funding; *Pfizer:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Agios Pharmaceuticals:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Biomarin:* Consultancy, Honoraria; *Roche:* Consultancy, Honoraria; *Novo Nordisk:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Hillhurst Biopharmaceuticals:* Membership on an entity's Board of Directors or advisory committees; *NHLBI:* Research Funding; *Sanofi:* Membership on an entity's Board of Directors or advisory committees; *Novartis:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Fulcrum Therapeutics:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Vertex:* Other: Data Monitoring Committee; *Takeda Pharmaceuticals:* Research Funding.

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Table 1. Baseline characteristics of the study cohort of adult SCD patients by persistent albuminuria.

	Persistent Albuminuria (N=104)	Without persistent albuminuria (N=164)
Age (yrs)	35 (28,44)	27.5 (23, 36.3)
Sex (F)	51 (49.0%)	102 (62.2%)
Weight (kg)	69.8 (62.6, 78.3)	66 (59, 78.5)
Height (cm)	170.2 (165, 178.3)	167.6 (161.9, 175.3)
Body mass index (kg/m^2)	23.2 (21.2, 27.8)	23 (20.7, 28.3)
Systolic blood pressure (mmHg)	122 (110, 138)	113 (108, 122)
Diastolic blood pressure (mmHg)	70 (65, 77)	67 (62, 73)
White blood cell count (10^9/L)	9.8 (7.3, 11.7)	7.9 (6.1, 10.4)
Hemoglobin (g/dL)	8.6 (7.5, 9.3)	9.1 (8.3, 10.1)
Platelet count (10^9/L)	357.5 (273.5, 462.3)	390 (264, 485)
Absolute reticulocyte count (10^9/L)	150.25 (0.39, 244.4)	135.55 (67.75, 239.8)
Hemoglobin F%	6.3 (3.5, 12.8)	10.1 (5.1, 15.6)
Hemoglobin S%	80.3 (71.6, 89.3)	80.6 (71.2, 85.5)
Total bilirubin (mg/dL)	2.8 (2, 4.7)	2.3 (1.6, 4.3)
Direct bilirubin (mg/dL)	0.5 (0.4. 0.8)	0.4 (0.3, 0.6)
Hemoglobinuria	14 (13.4%)	8 (4.8%)
eGFR CKD-EPI 2012-CysC (ml/min/1.73m^2)	110.8 (74.0, 128.0)	125.8 (107.7, 137.2)
Urine albumin:creatinine ratio (mg/g)	187.5 (96.7, 487)	12.2 (7, 21.1)
Pain crises in past 12 months	1 (0, 4)	1.3 (0.6, 2.6)
History of acute chest syndrome	70 (67.3%)	116 (70.7%)
History of stroke	14 (13.5%)	25 (15.2%)
History of leg ulcers	16 (15.4%)	8 (4.9%)
History of avascular necrosis	29 (27.9%)	42 (25.6%)
History of diabetes mellitus	3 (2.9%)	4 (2.4%)
Hydroxyurea use	78 (75%)	123 (75)
ACEi/ARB use	35 (33.7%)	11 (6.7%)
Other anti-hypertensive agent use	13 (12.5%)	7 (4.3%)
NSAID use	26 (25%)	85 (51.8%)

For continuous variables, median and interquartile range (IQR) are presented.
Abbreviations: eGFR CKD-EPI 2012-CysC = estimated glomerular filtration rate calculated using the CKD-EPI Cystatin C based equation ; ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; NSAID = non-steroidal anti-inflammatory drug

Table 2. Probability of persistent albuminuria by baseline UACR

Baseline UACR	Probability of persistent albuminuria
< 30 mg/g	0%
≥ 30 mg/g – 100 mg/g	54.9%
≥ 100 mg/g – 300 mg/g	81.8%
≥ 300 mg/g	84.2%

UACR = urine albumin-creatinine ratio
Persistent albuminuria – defined here as at least 2 of 3 values with UACR≥30 mg/g

Figure 1